2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of barium and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for barium based on toxicological studies and epidemiological investigations.

When evaluating the health effects of barium compounds, it is important to keep in mind that different barium compounds have different solubilities in water and body fluids and therefore serve as variable sources of the Ba^{2+} ion. The Ba^{2+} ion and the soluble compounds of barium (notably chloride, nitrate, hydroxide) are generally highly toxic to humans and experimental animals. The insoluble barium compounds (notably sulfate and carbonate) are inefficient sources of the Ba^{2+}, ion and therefore are generally nontoxic. Throughout the following section (2.2), the health effects by route of exposure of both soluble and insoluble barium compounds are discussed.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure

associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989c), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Studies evaluating the effects of barium following acute, intermediate, and chronic inhalation exposure are limited to several case reports of humans exposed occupationally (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988) and to two experimental studies with animals (Hicks et al. 1986; Tarasenko et al. 1977). These case reports and animal studies are not adequate for firmly establishing the health effects of barium by inhalation because of a number of significant study limitations. The case reports are generally inadequate because data were available for a limited number of exposed subjects and because exposure conditions (duration, frequency, dose) were not well characterized (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988). One of the two animal studies was limited in that apparently no control animals were used, an inhalation chamber providing a controlled dose and environment was not used, and there was a lack of information regarding the vehicle used, the purity of the test material, the duration and frequency of exposure, and the number of animals tested (Hicks et al. 1986). The second animal study consisted of several experiments but was generally limited in that the authors provided few details regarding experimental methods, exposure conditions, and test results, and no information as to the number of animals tested, the purity of the test material, or the statistical methods used; furthermore, in some experiments it was not clear whether or not control animals were used (Tarasenko et al. 1977). In view of the major limitations associated with the available case reports and animal studies, results from these reports should be regarded as providing only preliminary and/or suggestive evidence that acute, intermediate, and chronic inhalation exposure to barium may potentially be associated with adverse health effects. No reliable information was available

from any of the inhalation studies to identify NOAELs or LOAELs. Findings from the various case reports and animal studies are briefly described below.

2.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to barium.

2.2.1.2 Systemic Effects

No studies were located regarding dermal/ocular effects in humans or animals after inhalation exposure to barium.

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Respiratory Effects. Two studies of workers exposed chronically to dust from barium sulfate demonstrated that this exposure had a minor effect on the lungs. In one study, a benign pneumonoconiosis was observed in several factory workers (Doig 1976). In a second study in which workers were exposed by mining barium sulfate, silicosis was observed but was attributed to inhalation of quartz (Seaton et al. 1986). In contrast, a study of workers chronically exposed to barium carbonate dust reported no respiratory symptoms attributable to barium exposure (Essing et al. 1976). X-ray analysis of the lungs also showed no abnormalities attributable to barium dust.

Studies regarding respiratory effects in animals following inhalation exposure to barium are limited to two reports (Hicks et al. 1986; Tarasenko et al. 1977). Pulmonary lesions (perivascular and peribronchial sclerosis and focal thickening of the interalveolar septa) were observed in rats following intermediate inhalation exposure to 3.6 mg barium/m3 as barium carbonate dust (Tarasenko et al. 1977). Bronchoconstriction was reportedly noted in guinea pigs following inhalation for an unspecified period of time to 0.06 mg barium/m3/min as aerosolized barium chloride solution (Hicks et al. 1986).

Cardiovascular Effects. Three of 12 workers chronically exposed to barium carbonate dust had elevated blood pressure and 2 workers had ECG abnormalities (Essing et al. 1976). However, it is unknown whether this represented an increased incidence because no comparison with a control population was performed. Increased blood pressure and cardiac irregularities were reportedly observed in guinea pigs exposed by inhalation for an unspecified period of time to 0.06 mg barium/m3/min as aerosolized barium chloride solution (Hicks et al. 1986).

Gastrointestinal Effects. Abdominal cramps, nausea, and vomiting were experienced by a 22-year-old factory worker accidentally exposed by acute inhalation to a large but unspecified amount of barium carbonate powder (Shankle and Keane 1988). No animal studies were located regarding gastrointestinal effects in animals after inhalation exposure to barium.

Hematological Effects. Low serum potassium level was observed in a 22-year-old factory worker accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988). Altered hematological parameters were observed in rats following inhalation for an intermediate exposure period to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). Reported changes included decreased blood hemoglobin, decreased thrombocyte count, decreased blood glucose, decreased albumin, increased leukocyte count, and increased blood phosphorus.

Musculoskeletal Effects. After accidental exposure to a large amount of barium carbonate powder by acute inhalation, a 22-year-old factory worker developed progressive muscle weakness and paralysis of the extremities and neck (Shankle and Keane 1988). X-ray analysis of the bones and skeletal muscles of the pelvis and thighs of workers chronically exposed to barium carbonate dust revealed no apparent build up of barium in these tissues (Essing et al. 1976). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to barium.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to barium. Impaired detoxifying function of the liver was noted in one study in which rats were treated by intermediate inhalation exposure to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). No other details were reported.

Renal Effects. Renal failure occurred in a 22-year-old worker accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988). No studies were located regarding renal effects in animals after inhalation exposure to barium.

Other Systemic Effects. No studies were located regarding other systemic in humans after inhalation exposure to barium. Decreased body weight and decreased urinary calcium developed in rats following inhalation for an intermediate exposure period to 3.6 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to barium.

2.2.1.4 Neurological Effects

Absence of deep tendon reflexes was observed in a 22-year-old man accidentally exposed by acute inhalation to barium carbonate powder (Shankle and Keane 1988). No studies were located regarding neurological effects in animals after inhalation exposure to barium.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to barium. Only one limited report was available regarding developmental effects in animals after intermediate inhalation to barium (Tarasenko et al. 1977). Reduced survival, underdevelopment, lowered weight gain, and various hematologic alterations (erythropenia, leukocytosis, eosinophilia, neutrophilia) were reportedly noted in the offspring of female rats exposed by inhalation for an intermediate period to 2.2 or 9.4 mg barium/m^3 as barium carbonate dust (Tarasenko et al. 1977). No other significant details regarding this developmental study were reported.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to barium. Only one limited report was available regarding reproductive effects in animals following intermediate inhalation exposure to barium carbonate (Tarasenko et al. 1977). Disturbances in spermatogenesis, including decreased number of sperm, decreased percentage of motile sperm, and decreased osmotic resistance of sperm, were reportedly observed in male rats exposed by inhalation for one cycle of spermatogenesis to 15.8 mg barium/m^3 as barium carbonate dust. The testicles of these treated rats reportedly had an increase in the number of ducts with desquamated epithelium and a reduced number of ducts with 12^{th}-stage meiosis. The condition of the testicles of treated rats returned to normal 30 days after cessation of barium carbonate treatment (Tarasenko et al. 1977). Similar observations were noted in a second experiment in which male rats were exposed by inhalation for an intermediate period to 3.6 mg barium/m^3 as barium carbonate dust. In a third experiment by the same authors, female rats exposed by inhalation for an intermediate period to 2.2 or 9.4 mg barium/m^3 as barium carbonate dust reportedly developed a shortened estrous cycle and alterations in the morphological structure of the ovaries.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to barium. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to barium.

2.2.2 Oral Exposure

The majority of studies evaluating the health effects of barium are oral exposure studies. The available oral studies include numerous case reports of humans exposed orally to barium through accidental or intentional ingestion, several epidemiological and statistical investigations of humans exposed to drinking water containing barium, and various experimental animal studies involving acute, intermediate, or chronic exposure to barium either by gavage or by drinking water. In contrast to the limited inhalation studies that provide no reliable data to identify NOAELs and LOAELs, the available oral studies are more adequate for assessing the health effects of barium and provide reliable information to identify NOAEL and LOAEL values. Findings from the various oral studies are .summarized below.

2.2.2.1 Death

Death occurred in six cases of accidental or intentional ingestion of barium salts. Two deaths were due to cardiac arrest, one was due to severe gastrointestinal hemorrhage, and in three cases the specific cause was not determined (Das and Singh 1970; Diengott et al. 1964; McNally 1925; Ogen et al. 1967; Talwar and Sharma 1979). Doses in these cases were not known.

In addition to case reports of death in humans, several studies have examined mortality rates in humans exposed to drinking water contaminated with barium (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). Two of these studies examined the statistical correlation between barium concentrations in drinking water and total mortality and/or cardiovascular mortality rates in exposed populations (Elwood et al. 1974; Schroeder and Kraemer 1974). Negative correlations between barium and these mortality rates were found in both studies. These two particular studies are of limited use in assessing barium-induced mortality because of a number of study limitations, including a lack of information on exposure conditions (dose, duration, frequency) and the number of people exposed. Results of a third study indicated that relative to communities with little or no barium in drinking water, communities with elevated concentrations of barium in their drinking water had significantly higher mortality rates for all causes, heart disease, arteriosclerosis, and all cardiovascular disease (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981). This epidemiological study had a number of confounding variables, including possible use in the study population of home water softeners that would remove barium from the drinking water, inclusion of communities that had significant changes in population, lack of a way to control-for length of time an individual lived in a community, and widely varying concentrations of other contaminants (calcium, sodium, magnesium) in the drinking water. The human studies are not reliable for identifying NOAELs or LOAELs for death because of the limitations associated with these studies.

Mortality has been observed in experimental animals following acute and chronic oral exposure to barium chloride and barium acetate (Borzelleca et al. 1988; Schroeder and Mitchener 1975b; Tardiff et al. 1980). The acute oral LD_{50} was determined in one study to be 269 and 277 mg/kg (expressed as elemental barium) for female and male rats, respectively (Borzelleca et al. 1988). The acute oral LD_{50} in a second study was determined to be 132 and 220 mg/kg (expressed as elemental barium) for adult and weanling rats, respectively (Tardiff et al. 1980). These LD_{50} values (132 to 277 mg/kg) indicate that barium is toxic by acute oral gavage exposure to small experimental animals.

The studies evaluating mortality during intermediate and chronic oral exposure of experimental animals have provided mixed results. Reduced lifespan (approximately 11 percent) has been noted in male mice but not in female mice treated chronically with 0.95 mg barium/kg/day as barium acetate in drinking water (Schroeder and Mitchener 1975b). No significant effects *on* mortality were noted in an intermediate exposure study in which rats were treated with 35 mg barium/kg/day as barium chloride in drinking water (Tardiff et al. 1980). In a chronic study in which rats were treated with 0.7 mg barium/kg/day as barium acetate in drinking water, there were no significant effects on mortality (Schroeder and Mitchener 1975a). These mixed results may possibly be due to species differences.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1. LD_{50} values have also been recorded in Table 2-1 and Figure 2-1.

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. Respiratory weakness and paralysis requiring mechanical ventilation were frequently observed in cases of acute ingestion of barium salts by humans (Das and Singh 1970; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981).

Limited data are available regarding respiratory effects in animals following oral barium exposure. Acute gavage exposure of rats to 198 mg barium/kg/day as barium chloride has been associated with accumulation of fluid in the trachea; however, no pulmonary lesions upon gross necropsy and no changes in pulmonary weight were observed (Borzelleca et al. 1988). No changes in pulmonary weight were observed in a study in which rats were exposed for an intermediate period to doses less than 35 mg barium/kg/day as barium chloride in drinking water (Tardiff et al. 1980). Gross and

TABLE 2-1. Levels of Significant Exposure to Barium - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Ba/kg/day)	LOAEL (effect) Less serious (mg Ba/kg/day)	LOAEL (effect) Serious (mg Ba/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(GW)	1 d 1x/d				132 (LD_{50}, adult) 220 (LD_{50}, weanling)	Tarditf et al. 1980	$BaCl_2$
2	Rat	(GW)	1 d 1x/d				277 (LD_{50}, males) 269 (LD_{50}, females)	Borzelleca et al. 1988	$BaCl_2$
3	Rat	(GW)	1 d 1x/d				198 (death in 15/20 rats)	Borzelleca et al. 1988	$BaCl_2$
4	Rat	(GW)	10 d 1x/d				198 (death in 3/10 rats)	Borzelleca et al. 1988	$BaCl_2$
Systemic									
5	Rat	(GW)	1 d 1x/d	Resp		198 (fluid in trachea)		Borzelleca et al. 1988	$BaCl_2$
				Cardio	198				
				Gastro	66	198 (inflammation of intestines)			
				Hemato	198				
				Hepatic	66	198 (decreased liver/ brain weight ratio; darkened liver)			
				Renal	66	198 (increased kidney/ body weight ratio)			
				Other	66	198 (decreased body weight)			
Immunological									
6	Rat	(GW)	1 d 1x/d		198			Borzelleca et al. 1988	$BaCl_2$
7	Rat	(GW)	10 d 1x/d		198			Borzelleca et al. 1988	$BaCl_2$

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Ba/kg/day)	LOAEL (effect) Less serious (mg Ba/kg/day)	LOAEL (effect) Serious (mg Ba/kg/day)	Reference	Form
Neurological									
8	Rat	(GW)	1 d 1x/d		198			Borzelleca et al. 1988	$BaCl_2$
9	Rat	(GW)	10 d 1x/d		198			Borzelleca et al. 1988	$BaCl_2$
Reproductive									
10	Rat	(GW)	1 d 1x/d		198			Borzelleca et al. 1988	$BaCl_2$
11	Rat	(GW)	10 d 1x/d		138	198 (decreased ovaries weight and ovaries/ brain weight ratio)		Borzelleca et al. 1988	$BaCl_2$
INTERMEDIATE EXPOSURE									
Death									
12	Rat	(W)	13 wk 7d/wk		35			Tardiff et al. 1980	$BaCl_2$
Systemic									
13	Human	(W)	4 wk 7d/wk	Cardio	0.21			Wones et al. 1990	$BaCl_2$
14	Rat	(W)	1 mo 7d/wk	Cardio	0.71	7.1 (increased blood pressure)		Perry et al. 1983, 1985, 1989	$BaCl_2$
15	Rat	(W)	4 mo 7d/wk	Cardio	0.643	6.43 (increased blood pressure)		Perry et al. 1983, 1985, 1989	$BaCl_2$
16	Rat	(W)	13 wk 7d/wk	Resp	35			Tardiff et al. 1980	$BaCl_2$
				Cardio	35				
				Hemato	35				
				Musc/skel	35				
				Hepatic	35				
				Renal	35				
				Other	35				

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Ba/kg/day)	LOAEL (effect) Less serious (mg Ba/kg/day)	LOAEL (effect) Serious (mg Ba/kg/day)	Reference	Form
17	Rat	(W)	16 wk 7d/wk	Cardio Renal	15 15			McCauley et al. 1985	N.S.
Neurological									
18	Rat	(W)	13 wk 7d/wk		35			Tardiff et al. 1980	$BaCl_2$
CHRONIC EXPOSURE									
Death									
19	Rat	(W)	2 yr 7d/wk		0.7			Schroeder and Mitchener 1975a	$Ba(C_2H_3O_2)_2$
20	Mouse	(W)	2 yr 7d/wk				0.95 (reduced lifespan in males)	Schroeder and Mitchener 1975b	$Ba(C_2H_3O_2)_2$
Systemic									
21	Rat	(W)	2 yr 7d/wk	Resp Cardio Hepatic Renal	0.7 0.7 0.7 0.7			Schroeder and Mitchener 1975a	$Ba(C_2H_3O_2)_2$
22	Rat	(W)	16 mo 7d/wk	Cardio		5.4 (myocardial pathophysiologic and metabolic changes)		Kopp et al. 1985; Perry et al. 1983, 1985, 1989	$BaCl_2$
23	Rat	(W)	16 mo 7d/wk	Cardio	0.054	0.54 (increased blood pressure)		Perry et al. 1983, 1985, 1989	$BaCl_2$

TABLE 2-1 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg Ba/kg/day)	LOAEL (effect) Less serious (mg Ba/kg/day)	LOAEL (effect) Serious (mg Ba/kg/day)	Reference	Form
24	Mouse	(W)	2 yr 7d/wk	Other	0.95			Schroeder and Mitchener 1975b	$Ba(C_2H_3O_2)_2$

[a]The number corresponds to entries in Figure 2-1.

$Ba(C_2H_3O_2)_2$ = barium acetate; $BaCl_2$ = barium chloride; Cardio = cardiovascular; d = day; Gastro = gastrointestinal; GW = gavage-water; Hemato = hematological; LD_{50} = lethal dose, 50% kill; *mo* = *month*; Musc/skel = musculoskeletal; N.S. = not specified; Resp = respiratory; W = drinking water; wk = week; x = time(s); yr = year

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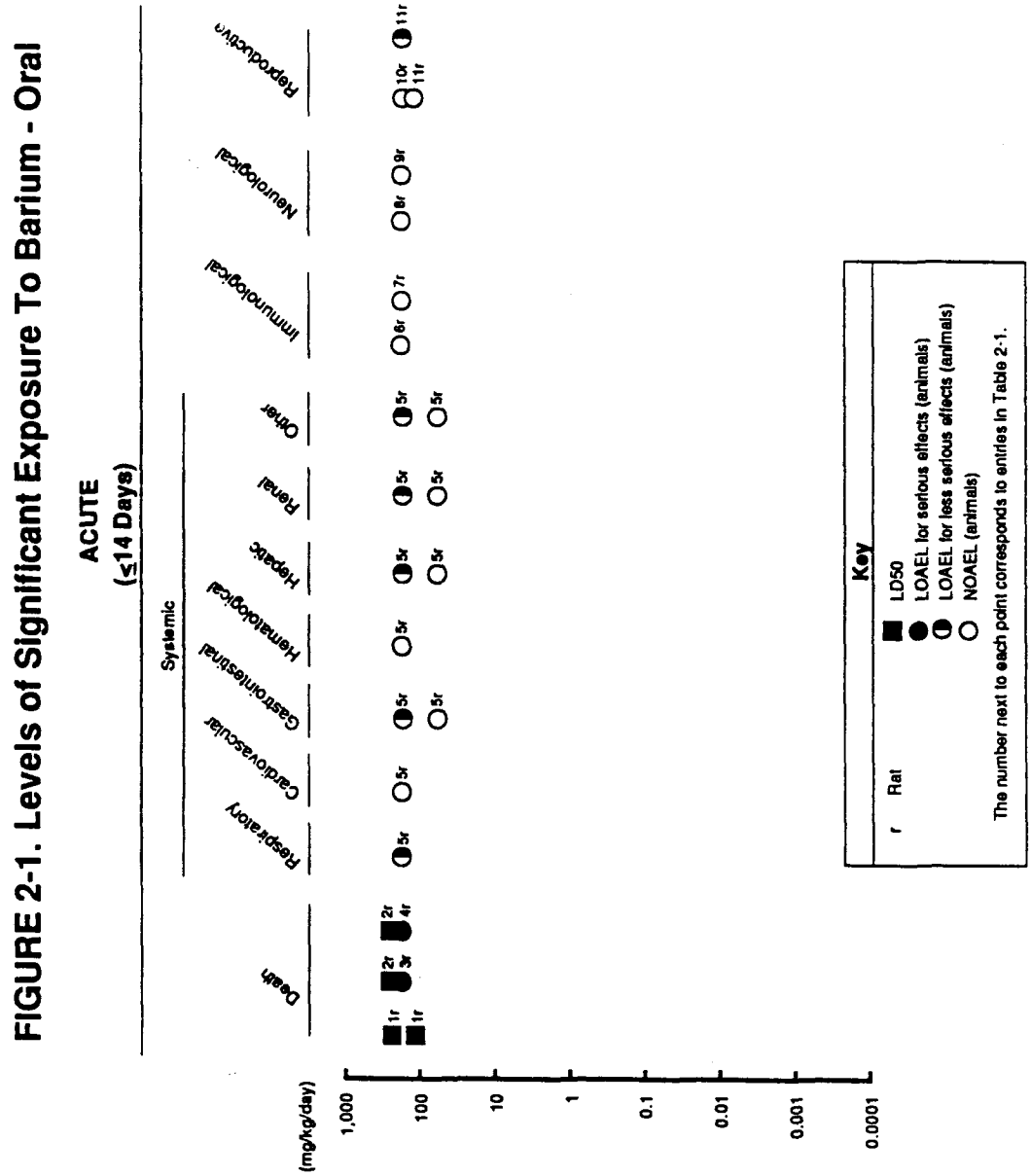
FIGURE 2-1. Levels of Significant Exposure to Barium - Oral



2. HEALTH EFFECTS

FIGURE 2-1 (Continued)

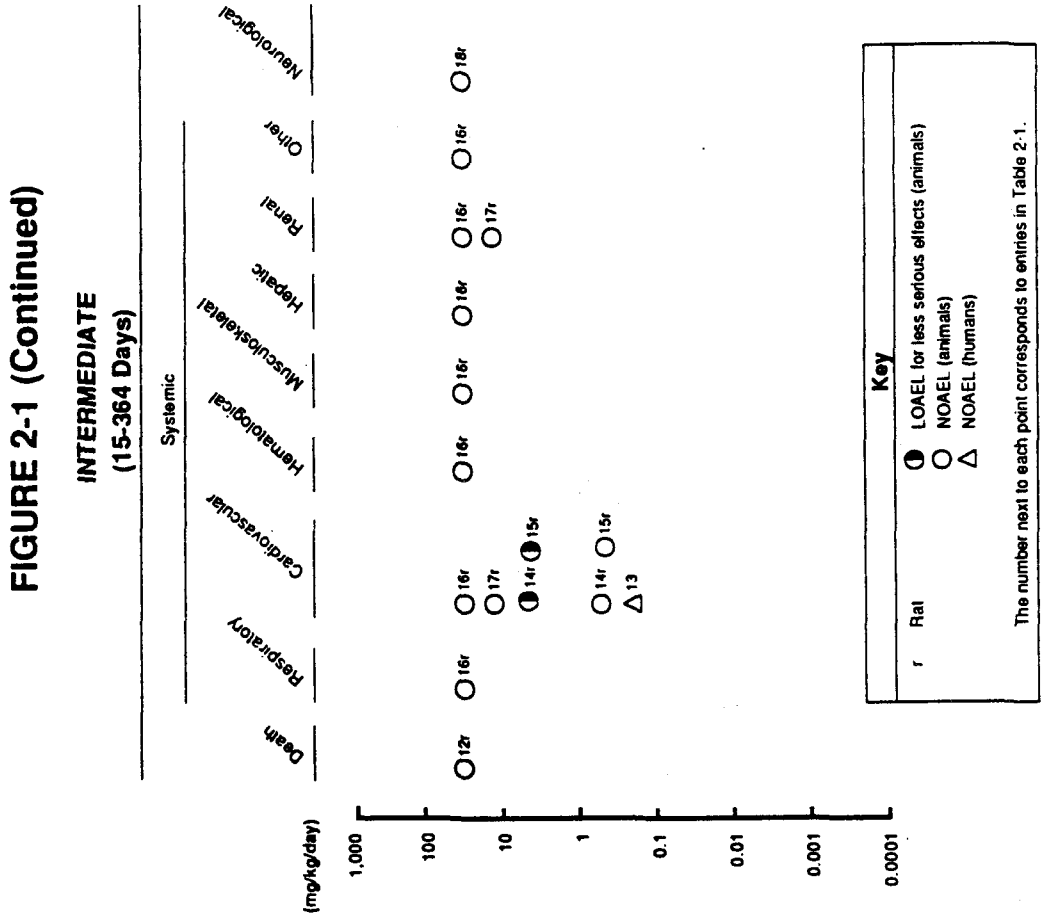
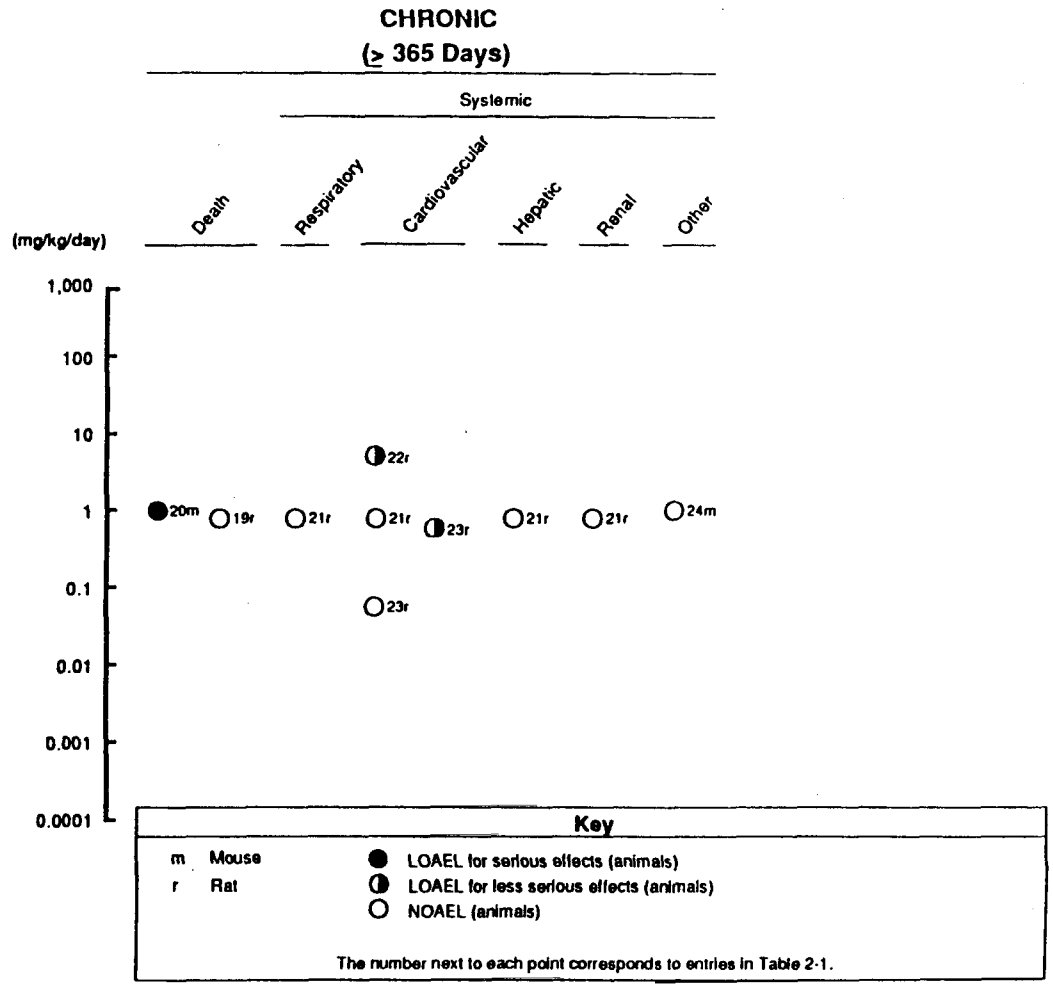


FIGURE 2-1 (Continued)



histopathological lesions of the lung have not been observed in rats exposed to 0.7 mg barium/kg/day as barium acetate in drinking water for lifetime (Schroeder and Mitchener 1975a).

Cardiovascular Effects. The most commonly observed cardiovascular effects in cases of acute ingestion of barium compounds are hypertension and abnormalities in heart rhythm (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Wetherill et al. 1981). Myocardial damage was observed in a few cases (Lewi and Bar-Khayim 1964; McNally 1925; Talwar and Sharma 1979). Ln one atypical case, hypotension was observed (Talwar and Sharma 1979).

No adverse effects on blood pressure or cardiac rhythms were observed in a study in which volunteers consumed 0.21 mg barium/kg/day for 4 weeks (Wones et al. 1990). In this study, the subjects' preexposure blood pressure and cardiac rhythm served as the control for comparison with postexposure values. This study is somewhat limited in that the number of subjects evaluated was small (n=11) and the absorption and/or serum levels of barium were not assessed. An epidemiological study of communities consuming drinking water containing elevated barium levels also did not provide evidence that chronic exposure to barium in drinking water was associated with increased blood pressure, hypertension, stroke, heart disease, *or* altered electrocardiograms (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981). However, this study is limited in that blood pressure was determined in a single 20-minute session and not followed over a longer period (e.g., months, years), exposure conditions were not well-characterized (duration, frequency), individual exposure doses were not determined, and the incidence of hypertension, stroke, and heart disease was determined by responses to a survey questionnaire and not by testing and/or diagnosis.

Cardiovascular effects have been evaluated in acute, intermediate, and chronic oral studies with experimental animals. Acute studies have been limited to histological examination of the heart following 1-day or 10-day gavage exposure of rats to doses as high as 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988). No microscopic lesions of the heart were observed. Other cardiovascular parameters were not evaluated.

Results from several studies with experimental animals indicate that intermediate and chronic oral exposure to barium is associated with adverse cardiovascular effects (Kopp et al. 1985; Perry et al. 1983, 1985, 1989). In a series of experiments, rats were administered barium chloride in drinking water either for 1, 4, or 16 months (Perry et al. 1983, 1985, 1989). Elemental barium doses in the l-month study were either 0, 0.071, 0.71, or 7.1 mg/kg/day. Elemental barium doses in the 4-month study were either 0, 0.0643, 0.643, or 6.43 mg/kg/day. Elemental barium doses in the 16-month study were either 0, 0.054, 0.54, or 5.4 mg/kg/day. In the l-month study, significant increases in blood pressure were noted in rats treated with 7.1 mg/kg/day; no change in blood pressure was noted in rats treated with

either 0.071, or 0.71 mg/kg/day. In the 4-month study, significant increases in blood pressure were observed in rats treated with 6.43 mg/kg/day; no change in blood pressure was observed in rats treated with either 0.0643 or 0.643 mg/kg/day. Significant increases in blood pressure also were noted in the 16-month study in rats treated with 0.54 and 5.4 mg/kg/day; however, no effects on blood pressure were noted in the 16-month experiment at 0.054 mg/kg/day. The high-dose group (5.4 mg/kg/day) exposed for 16 months also had depressed cardiac contraction, depressed cardiac electrical conductivity, and decreased cardiac ATP, phosphocreatine, and phosphorylation potential (Kopp et al. 1985; Perry et al. 1983, 1985, 1989).

In contrast to the studies by Perry et al. (1983, 1985, 1989), increased blood pressure was not observed in one study in which barium was administered to normotensive rats for an intermediate period at doses up to 15 mg/kg/day in either drinking water or in 0.9% saline (McCauley et al. 1985). The reason for the discrepancy between the results of the studies by Perry et al. (1983, 1985, 1989) and the study by McCauley et al. (1985) is not known. As in the Perry et al. (1983, 1985, 1989) studies, the rats in the study by McCauley et al. (1985) were maintained on a diet low in barium content. However, it was not reported by McCauley et al. (1985) whether or not this low barium diet contained certain other trace metals. Certain metals such as sodium and potassium can potentially influence blood pressure.

In other studies with rats, intermediate and chronic oral exposure to barium chloride and barium acetate in drinking water have not been associated with any changes in heart weight or with any gross or microscopic Lesions of the heart (Schroeder and Mitchener 1975a; Tardiff et al. 1980).

Additional experiments using uninephrectomized and specially bred Dahl salt-sensitive and salt-resistant strains of rats revealed no adverse effects on blood pressure resulting from 16 weeks of exposure to barium doses as high as 150 mg/kg/day (McCauley et al. 1985). However, no untreated controls were used in these experiments; thus, these results must be interpreted with caution. Interestingly, Dahl salt-sensitive rats treated with 15 or 150 mg barium/kg/day did not experience the normal hypertensive response when given 0.9% NaCl-containing drinking water. Experiments assessing the effect of a 5-month exposure to barium on the cardiac response to an arrythmagenic challenge with 1-norepinephrine demonstrated a significant increase in reflex bradycardia when rats were given 37.5 mg barium/kg/day in their drinking water (McCauley et al. 1985). However, this experiment was confounded by the presence of barium in the diet of both control and treated animals (estimated barium intake from diet consumption = 1 mg/kg/day). Without adequate controls these experiments are difficult to interpret.

Gastrointestinal Effects. All cases of acute oral barium poisoning in adults exhibit gastrointestinal disturbances as the initial symptoms. These include gastric pain, vomiting, and diarrhea (Das and Singh 1970; Diengott et

al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen *et* al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). In one case, severe gastrointestinal hemorrhage occurred in an adult male victim (Diengott et al. 1964).

Gastrointestinal effects also have been observed in animals, but the reliable animal data are limited. Inflammation of the intestines was noted in rats acutely exposed by gavage to doses of 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988). Stomach rupture, bowel obstruction, and gastrointestinal hemorrhage have been observed in rats in a separate study involving acute oral exposure to barium sulfate; however, those adverse effects were most likely due to the massive doses used in the study (25%-40% of body weight) and not necessarily to barium sulfate toxicity (Boyd and Abel 1966). No gross or microscopic lesions of the esophagus, stomach, pancreas, small intestines, or colon were noted in several intermediate and chronic experiments in which rats were exposed to doses as high as 37.5 mg barium/kg/day of an unspecified barium compound in drinking water; however, interpretation of these experiments is confounded by the presence of barium as a contaminant in the rat chow and the resulting lack of an "untreated" control group (McCauley et al. 1985). Actual oral exposure doses cannot be reliably determined from these particular intermediate and chronic studies but may be estimated at up to 38.5 mg barium/kg/day by adding the estimated intake from the contaminated chow (1 mg barium/kg/day) to the dose in the drinking water.

Hematological Effects. In human case studies of oral barium poisoning, a decrease in serum potassium is frequently observed in the subjects (Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981).

The effect of oral barium exposure on various blood chemistry parameters that are important for cardiovascular function has been evaluated in only one experimental study with humans (Wones et al. 1990). In this study, 0.2 mg barium/kg/day as barium chloride was supplied in the drinking water of subjects for 4 weeks. No clinically significant changes were noted in any of the blood chemistry parameters monitored (total plasma cholesterol; plasma triglycerides; plasma HDL and LDL cholesterol; plasma apolipoproteins; and serum glucose, potassium, calcium, and albumin). However, this study is limited in that the number of subjects evaluated was small (n-11) and absorption and/or serum levels of barium were not assessed.

Results of animal studies indicate that acute, intermediate, and chronic oral exposure to barium is not associated with any adverse hematological effects. In an acute study in which groups of rats were exposed by gavage to four doses ranging from 66 to 198 mg barium/kg/day as barium chloride, hematological and blood chemistry parameters did not significantly change or could not be attributed to barium exposure (erythrocyte, leukocyte, platelet, and differential leukocyte count; hematocrit; hemoglobin; prothrombin time;

plasma fibrinogen; serum protein, albumin, globulin, bilirubin. creatine, calcium, phosphorus, chloride, 5'-nucleotidase, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and alkaline phosphatase) (Borzelleca et al. 1988). Intermediate and chronic oral exposure of rats to barium acetate and barium chloride in drinking water has not been associated with any significant or treatment-related changes in a variety,of hematological parameters (Schroeder and Mitchener 1975a; Tardiff et al. 1980). Elemental barium doses in these intermediate and chronic drinking water studies ranged from 0.7 mg/kg/day to 35 mg/kg/day.

Musculoskeletal Effects. The predominant musculoskeletal effect observed in cases of barium toxicity in humans is progressive muscle weakness, often leading to partial or total paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). In severe cases, the paralysis affects the respiratory system (Das and Singh 1970; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981).

Very limited animal data are available regarding the musculoskeletal effects of barium following oral exposure. No changes in femur weight and no gross or microscopic lesions of the femur were observed in rats following intermediate exposure to doses of 35 mg barium/kg/day as barium chloride in drinking water (Tardiff et al. 1980). Gross and microscopic lesions of the sternebrae and femur were not observed in several intermediate and chronic experiments in which rats were exposed to an unspecified barium compound in drinking water (McCauley et al. 1985). However, these experiments were flawed in that barium was detected as a contaminant in the rat chow of both control and treated animals; consequently, no true "untreated" controls were available for comparison. Thus, the results should be interpreted with caution.

Hepatic Effects. In one case study involving accidental acute ingestion of barium carbonate in an adult female, some degeneration of the liver was noted post-mortem .(McNally 1925). Adverse hepatic effects in animals following oral barium exposure have been minor or have not been observed. Decreased liver/brain weight ratio and darkened liver were observed in rats exposed acutely by gavage to 198 mg barium/kg/day as barium chloride; however, these changes were not associated with any microscopic hepatic lesions (Borzelleca et al. 1988). Acute gavage exposure of rats to four doses ranging from 66 to 198 mg barium/kg/day as barium chloride was not associated with any significant changes in the activities of serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), or alkaline phosphatase (ALP) (Borzelleca et al. 1988). Changes in these enzyme levels in blood can be indicative of liver damage. Significantly reduced blood urea nitrogen was noted at all exposure doses. A reduction in this particular blood chemistry parameter is a potential sign of altered liver function. However, insufficient information was presented in the published study to

determine if the reduced blood urea nitrogen was an adverse liver effect. Results of intermediate and chronic studies involving oral exposure of rats to barium in drinking water have been negative for hepatic effects (Schroeder and Mitchener 1975a; Tardiff et al. 1980). In these intermediate and chronic studies, hepatic effects were assessed by determining hepatic weight and by performing gross and histopathological examinations of the liver.

Renal Effects. Toxic effects on the kidneys have been observed in several adult cases of acute barium poisoning. Effects include hemoglobin in the urine (Gould et al. 1973), renal insufficiency (Lewi and Bar-Khayim 1964; Phelan et al. 1984), degeneration of the kidneys (McNally 1925), and acute renal failure (Wetherill et al. 1981).

Renal effects observed in animals following oral barium exposure have been minor. Increased kidney/body weight ratios have been noted in rats exposed acutely by gavage to 198 mg barium/kg/day as barium chloride; however, this change was not associated with gross or microscopic renal lesions (Borzelleca et al. 1988).

Results of intermediate and chronic studies in which rats have been exposed orally to barium drinking water have been negative for renal effects (McCauley et al. 1985; Schroeder and Mitchener 1975a; Tardiff et al. 1980). In these intermediate and chronic studies, renal effects were evaluated by determining kidney weight and by performing gross and/or histopathologic examination of the kidney. Lesions of the renal glomeruli were reportedly observed in several experiments involving oral exposure of uninephrectomized rats and salt-sensitive and salt-resistant rats to 150 mg barium/kg/day of an unspecified barium compound for 16 weeks; however, these particular experiments are inconclusive regarding renal toxicity because no control animals were used (McCauley et al. 1985).

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to barium. In studies with Sprague-Dawley rats, both ocular discharge following acute oral exposure to barium chloride (Borzelleca et al. 1988) and a nonsignificant increase in retinal dystrophy following intermediate and chronic oral exposure to an unspecified barium compound (McCauley et al. 1985) have been observed. Although the retinal dystrophy was statistically insignificant, a dose-related trend was observed if different duration exposure groups were combined (McCauley et al. 1985). Both ocular discharge and retinal dystrophy are commonly observed in Sprague-Dawley rats; consequently, the ocular lesions noted in these animal studies can not necessarily be attributed to oral barium exposure.

Other Systemic Effects. In one human case study involving accidental acute ingestion of barium carbonate by an adult female, some degeneration of the spleen was noted post-mortem (McNally 1925). Body weight has been monitored in a number of acute, intermediate, and chronic studies in which

rats and mice were exposed orally to barium compounds (Borzelleca et al. 1988; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a, 1975b; Tardiff et al. 1980). A change in body weight was observed in only one of these studies (Borzelleca et al. 1988). In this one study, decreased body weight was noted in rats given a single gavage dose of 198 mg barium/kg/day as barium chloride (Borzelleca et al. 1988). Limited data are available on other systemic effects of barium. In one intermediate drinking water study with rats, no gross or microscopic lesions of the adrenals were noted at doses up to 35 mg barium/kg/day as barium chloride (Tardiff et al. 1980).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to barium. Animal data regarding immunological effects following oral exposure are very limited. Acute gavage exposure of rats to doses less than 198 mg barium/kg/day as barium chloride was not associated with any changes in thymus weight or any gross lesions of the thymus (Borzelleca et al. 1988). Intermediate and chronic oral exposure of rats to nominal concentrations of barium in drinking water of 37.5 and 15 mg/kg/day, respectively, was not associated with lesions of the lymph nodes or thymus upon gross and histopathologic examination (McCauley et al. 1985). However, this latter study is of limited value for evaluating the effects of barium because the barium compound tested was not specified and the chow used to feed the rats was contaminated with 12 ppm barium; thus, no true "untreated" control group was available for comparison.

The highest NOAEL values for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.4 Neurological Effects

Numbness and tingling around the mouth and neck were sometimes among the first symptoms of barium toxicity in humans (Lewi and Bar-Khayim 1964; Morton 1945). Occasionally, these neurological symptoms extended to the extremities (Das and Singh 1970; Lewi and Bar-Khayim 1964). Partial and complete paralysis occurred in severe cases, often accompanied by an absence of deep tendon reflexes (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Post-mortem examination in one case of poisoning by ingestion of barium sulfide revealed brain congestion and edema (McNally 1925).

Animal studies evaluating the neurological effects of barium following oral exposure are limited to three reports (Borzelleca et al. 1988; McCauley et al. 1985; Tardiff et al. 1980). Acute gavage exposure of rats to doses as high as 198 mg barium/kg/day as barium chloride was not associated with changes in brain weight or with any gross lesions of the brain (Borzelleca et al. 1988). Intermediate oral exposure of rats to nominal doses less than

37.5 mg barium/kg/day in drinking water was not associated with lesions of the brain upon gross and microscopic examination (McCauley et al. 1985; Tardiff et al. 1980), or with any changes in brain weight (Tardiff et al. 1980). No lesions of the brain were observed in rats following chronic oral exposure to nominal doses of 15 mg barium/kg/day in drinking water (McCauley et al. 1985). The intermediate and chronic drinking water studies are of limited value for assessing the effects of barium on the brain because the barium compound tested was not specified and because the chow used to feed the rats was contaminated with 12 ppm barium; thus, no true "untreated" control group was available for comparison.

The highest NOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.5 Developmental Effects

Studies regarding developmental effects of barium following oral exposure are limited to one human study (Morton et al. 1976) and one animal study (Tarasenko et al. 1977). A statistically significant negative correlation was found between barium concentrations in drinking water and human congenital malformation rates of the central nervous system in South Wales (Morton et al. 1976). A negative correlation implies that as the barium concentration in drinking water increased, the rate of central nervous system malformations decreased. This statistical study is of limited value in identifying a NOAEL for developmental effects because exposure conditions (duration and frequency of exposure, dose, number of subjects exposed) were not characterized.

Developmental effects were reported in one study in which female rats were treated orally during conception and pregnancy with approximately 18.3 mg barium/kg/day as barium carbonate (Tarasenko et al. 1977). Reported effects in offspring included increased mortality, increased leukocyte count, disturbances in liver function, and increased urinary excretion of hippuric acid. The latter study is inadequate for evaluating developmental effects of oral barium exposure because of major study limitations. These limitations include a general lack of information provided by the authors regarding experimental methods, exposure conditions, and test results, and no information as to the number of animals tested, the purity of the test material, the statistical methods used, and whether or not controls were used. No other animal studies evaluating developmental effects were available.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to barium. However, limited data are available from acute, intermediate, and chronic animal studies in which certain reproductive organs were weighed and examined grossly and microscopically following oral barium exposure. Acute gavage exposure of rats to doses as low as 198 mg

barium/kg/day as barium chloride has been associated with decreased ovary weight and decreased ovary/brain weight ratio; however, no changes in testicular weight and no gross lesions of the ovaries or testes were observed at this dose (Borzelleca et al. 1988). No adverse effects in these parameters were noted at doses as high as 135 mg barium/kg/day. Intermediate and chronic oral exposure of rats to nominal concentrations of barium in drinking water of 37.5 or 15 mg/kg/day, respectively, was not associated with any gross or histopathologic lesions of the uterus, ovaries, or testes (McCauley et al. 1985). However, this latter study is of limited value for identifying a NOAEL for barium because the barium compound tested was not specified and because the chow used to feed the rats was contaminated with 12 ppm barium; thus, no true "untreated" control group was available for comparison. No animal studies were available that assessed reproductive function following oral barium exposure.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxicity in humans or animals after oral exposure to barium. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to barium. Only two animal studies evaluated the induction of tumors following chronic oral exposure to barium (Schroeder and Mitchener 1975a, 1975b). In these two studies, rats and mice were exposed to 0.7 and 0.95 mg barium/kg/day, respectively, as barium acetate in drinking water for lifetime. Organs and tissues were examined grossly and microscopically; organs examined microscopically were limited to heart, lung, liver, kidney, and spleen. No differences in the incidence of tumors were noted between treated animals and vehicle controls in either study. These two studies are inadequate for evaluating the carcinogenic potential of barium because insufficient numbers of animals were used for a carcinogenicity study, it was not determined whether or not a maximum tolerated dose was achieved, a complete histological examination was not performed, the purity of the test material was not specified, and only one exposure dose was used in each study.

2.2.3 Dermal Exposure

Limited information is available regarding the health effects of barium following dermal exposure. Barium salts would be expected to have a local effect on skin surfaces and would not likely be absorbed systematically to any great extent. Available studies include a case report of an individual exposed

dermally to molten barium chloride (Stewart and Hummel 1984), a skin irritation study evaluating barium carbonate in experimental animals (Tarasenko et al. 1977), and a skin-painting study in which mice were exposed dermally to a barium hydroxide extract of tobacco leaf (Van Duuren et al. 1968). No reliable information was available from any of these dermal studies to identify study NOAELs or LOAELs for barium. In the case report (Stewart and Hummel 1984), the dermal burns that developed in the individual exposed to molten barium chloride may potentially have contributed to some of the reported health effects, which are described briefly in Section 2.2.3.2 (Systemic Effects).

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to barium.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to barium.

Cardiovascular Effects. An abnormal electrocardiogram was observed in a 62-year-old man burned by molten barium chloride (Stewart and Hummel 1984). No studies were located regarding cardiovascular effects in animals after dermal exposure to barium.

Gastrointestinal Effects. A 62-year-old man experienced vomiting after he was accidentally burned by molten barium chloride (Stewart and Hummel 1984). No studies were located regarding gastrointestinal effects in animals after dermal exposure to barium.

Hematological Effects. A 62-year-old victim accidentally exposed to molten barium chloride had a depressed plasma potassium level and an increased plasma barium level when admitted to the hospital (Stewart and Hammel 1984). No studies were located regarding hematological effects in animals after dermal exposure to barium.

Dermal/Ocular Effects. Molten barium chloride induced burns on the skin of a 62-year-old man who was accidentally exposed through an explosion. The dermal burns, however, were very probably due to the molten nature of the material and not necessarily to barium chloride (Stewart and Hammel 1984).

The dermal and ocular effects of barium carbonate were examined in a study with rats and rabbits (Tarasenko et al. 1977). When barium carbonate in lanolin was applied to the skin, ulcers developed. These dermal lesions reportedly disappeared within a month when dermal treatment was discontinued. When barium carbonate powder was introduced into the conjunctival sac,

purulent discharge, conjunctivitis, and slight opacity of the cornea developed. Although these findings suggest that barium carbonate may be a dermal and ocular irritant, these particular investigations are inadequate for establishing the dermal and ocular effects of barium because of a number of significant study limitations. The authors provided few details regarding experimental methods and results, and no information as to the concentration of barium carbonate used, the number of animals used, and whether or not controls were used. Furthermore, rats are not typically used to evaluate the skin and eye irritating effects of compounds.

No studies were located regarding the following health effects in humans or animals after dermal exposure to barium:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to barium. Dysplasia of the cervical epithelium was reportedly induced in a woman who had a barium chloride solution applied to her cervix (Ayre 1966). The use of dimethyl sulfoxide in combination with the barium chloride solution reportedly enhanced the ability of barium chloride to induce dysplasia. Dysplasia can be regarded as a potential precancerous lesion. The significance of the observations reported in this study are difficult to assess, since only one subject was exposed and because there have been no reports of similar findings in other human or animal studies. Also, the vehicle used was not specified in this study.

No studies were located regarding cancer in animals after dermal exposure to barium. However, results of one skin-painting study with mice suggest that barium hydroxide extract derived from tobacco leaf may act as a tumor-promoting agent (Van Duuren et al. 1968). In this study, mice were treated dermally for an unspecified period of time with either barium hydroxide extract alone, 7,12-dimethylbenz(a)anthracene (DMBA) alone (an initiating agent), or a combination of DMBA and barium hydroxide extract. After 1 year, none of the mice treated with barium hydroxide extract developed skin tumors. However, 3 out of 20 mice treated with DMBA alone and 7 out of 20 mice treated with a combination of both barium hydroxide extract and DMBA developed skin papillomas and carcinomas. These results provide limited, but suggestive evidence that barium hydroxide extract of tobacco leaf acted as a tumor-promoting agent. However, it can not be determined whether or not this

apparent positive tumorigenic response was due to barium hydroxide or some other component of the barium hydroxide tobacco leaf extract.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption of barium in humans following inhalation exposure: However, results of studies with experimental animals suggest that the rate and extent of absorption of barium from the respiratory tract depends on the exposure level, how much barium reaches the alveolar spaces, the clearance rate from the upper respiratory tract, and the solubility of the particular form of barium that was administered.

The results of a hamster study indicated that after inhalation of barium chloride, 65% of the administered dose was deposited in the nasal region and was eventually absorbed into the body (Cuddihy and Ozog 1973b). Radioactive barium sulfate that is injected directly into the trachea of rats can be taken up into the epithelium membranes, and remain in these membranes for at least a few weeks (Gore and Patrick 1982; Takahashi and Patrick 1987). These studies have also shown that barium in the trachea can be cleared to the lymphatic system (Takahashi and Patrick 1987).

Results of experiments with dogs have indicated that, following inhalation of barium chloride or barium sulfate, approximately half of the barium chloride dose and three-fourths of the barium sulfate dose are deposited in the pulmonary region (Cuddihy et al. 1974). About one-fourth of the absorbed barium is transported to the skeleton, the remainder is excreted in the urine and feces within 2 weeks. The biological half life of radioactive barium sulfate in the pulmonary region has been calculated to be 8 days in the dog (Morrow et al. 1964) and 10 days in the rat (Cember et al. 1961). Total body deposition in dogs that inhaled radioactive barium chloride was found to be 51% of the total inhaled activity, indicating that at least this much was absorbed (Morrow et al. 1964). Experiments in rats exposed to barium sulfate via intratracheal injection have shown that about 7% of the initial lung burden was finally cleared to the blood (Spritzer and Watson 1964).

2.3.1.2 Oral Exposure

As with other metals, barium is probably very poorly absorbed from the gastrointestinal tract. The International Commission for Radiation Protection (ICRP) estimates that the gastrointestinal absorption of barium is less than 5% (ICRP 1973). This percentage is supported by studies of two men whose daily input and fecal excretion were monitored for 50 weeks (Tipton et al. 1969).

Experiments in rats have shown that younger animals (22 days old or less) absorb about 10 times more barium chloride from the gastrointestinal tract (63%-84%) than do older animals (about 7%) (Taylor et al. 1962). Starved adult rats absorb a bit more (20%). Gastrointestinal absorption in dogs has been calculated to be about 7% (Cuddihy and Griffith 1972). Measurements of barium in the serum indicate that the peak absorption from the gastrointestinal system is within 1 hour in dogs (Chou and Chin 1943). Similar results were seen in rats given various barium compounds (McCauley and Washington 1983).

2.3.1.3 Dermal Exposure

No studies were located regarding absorption of barium in humans after dermal exposure. One animal study showed that barium applied to the skin of piglets was found in the various layers of the skin (Shvydko et al. 1971). Barium is not expected to cross the intact skin because of the high polarity of the forms in which it is most commonly encountered.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Studies in humans indicate that barium distributes predominantly to the skeleton and teeth. The route of exposure is not always known, but it is presumed to be mostly oral; therefore, the studies are discussed below in Section 2.3.2.2.

Dogs that inhaled radiolabeled barium chloride had about 70% of the initial body burden in the lungs and internal organs. Of this, most was in the skeleton (44%), and urine and feces (13% each). Very little was found in the blood (1%) and muscle (4%) (Cuddihy and Griffith 1972).

2.3.2.2 Oral Exposure

Humans can be exposed to barium in the air, water, or food. Numerous studies exist that discuss the distribution of barium in the human body, but they do not always specify route of exposure. It is presumed that the majority of the barium intake is from the oral route. Barium occurs mostly (over 93%) in the bones and teeth of humans. Very little is found in blood plasma or soft tissues; but, when it is detected in the organs, it is found in the eye, lungs, skin, and adipose tissue in humans at less than 1% of total body weight (Schroeder et al. 1972). This information is supported by a number of studies (Bauer et al. 1957; Losee et al. 1974; Miller et al. 1985; Moloukhia and Ahmed 1979; Sowden 1958; Sowden and Stitch 1957; Sowden and Pirie 1958).

Rats that ate barium chloride as a component of Brazil nuts showed an accumulation in the skeleton (Stoewsand et al. 1988). Rats that were given

various barium compounds in the drinking water showed distribution to the heart > eye > skeletal muscle > kidney > blood > liver. The skeleton was not examined (McCauley and Washington 1983).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of barium in humans or animals after dermal exposure.

2.3.3 Metabolism

Barium is not metabolized in the body, but it may be metabolically transported or incorporated into complexes or tissues.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies have been located regarding excretion of barium following inhalation exposure in humans. In dogs that inhaled radiolabeled barium chloride, less than 1% of the initial body burden remained in the body after 5 days. Fecal excretion was about twice that of urinary excretion (Cuddihy and Griffith 1972).

2.3.4.2 Oral Exposure

Barium taken by mouth is poorly absorbed; therefore, most of the dose is excreted in the feces. Case studies have shown that excretion of oral doses of humans is about 3% in the urine, and most of the remainder in the feces (Tipton et al. 1966).

Dogs that received barium by gavage excreted most of the dose within a few days and less than 3% of the initial body burden remained in the body after 2 weeks (Cuddihy and Griffith 1972).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of barium in humans or animals after dermal exposure.

2.3.4.4 Other Routes of Exposure

Humans who have had intravenous injections of barium excrete barium in the feces. A man who was injected with barium intravenously excreted most of the dose in the feces (Newton et al. 1977). Another case study showed that about 9% of an intravenous dose of barium was excreted in the urine, and about 84% in the feces (Harrison et al. 1967).

Animal studies have also shown secretion of radioactive barium into the stomach and intestines following intravenous injection (Syed et al. 1981). The plasma clearance of barium following intravenous injection over 9 days has been demonstrated in rabbits to be 62 ml/hour in the urine and 170 ml/hour in the feces (Liniecki 1971). The total excretion after 9 days was about 50%.

2.4 RELEVANCE TO PUBLIC HEALTH

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for barium because studies evaluating the effects of barium in humans and animals following acute, intermediate, and chronic inhalation exposure were inadequate for establishing the exposure concentrations associated with adverse health effects. The human studies (Doig 1976; Easing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988) were limited by the small number of subjects and the lack of quantitative exposure information. The animal studies (Hicks et al. 1986; Tarasenko et al. 1977) were limited by inadequate descriptions of the experimental design.

No acute-, intermediate-, or chronic-duration oral MRLs were derived for barium because of limitations of the studies evaluating oral exposure to barium for such durations. Case studies of acute exposures in humans did not provide adequate characterization of the doses associated with adverse health effects and acute-duration animal studies did not provide sufficient data to identify a target organ.

Intermediate-duration oral studies in humans either did not provide adequate characterization of doses associated with adverse health effects (Brenniman and Levy 1985; Brenniman et al. 1979a, 1981) or the number of subjects examined was too small (Wanes et al. 1990). The observation of increased blood pressure in an intermediate-duration oral study in rats (Perry et al. 1983, 1985, 1989) was not used to set an MRL because the resulting MRL would be approximately 1.5-4-fold lower than the estimated daily intake of barium from air, water, and dietary sources combined.

No chronic-duration oral KRL was established for barium, despite the observation of a NOAEL and a LOAEL for blood pressure effects in a ChrOniC rat study by Perry et al. (1983, 1985, 1989), because the resulting MRL would have been approximately 19-50-fold lower than the estimated daily intake of barium from air, water, and dietary sources combined.

No acute-, intermediate-, or chronic-duration dermal MRLs were derived for barium because of the lack of an appropriate methodology for the development of dermal MRLs.

Barium is naturally present to some extent in water and food. Consequently, the general population is exposed normally to barium through the ingestion of drinking water or food. The general population also is exposed by inhalation to low levels of barium in ambient air. Exposure to barium

through public drinking water supplies, food, or ambient air generally should not pose a significant health risk to humans because of the very low levels of barium that would typically be associated with these types of exposures.

Since barium is a frequent contaminant at hazardous waste sites, humans living or working near these sites may potentially become exposed to barium. Concentrations of barium in soil or groundwater may be significantly elevated over background levels at hazardous waste sites, thereby posing a potential health risk to humans. Soil contaminated with barium is of concern because airborne dusts generated from contaminated surface soil through the action of wind may potentially expose individuals by inhalation. Airborne barium dusts generated from contaminated surface soil could potentially form residues on foods that are ingested. There is also the potential that children may ingest barium through hand to mouth contact following playing in contaminated soil. Groundwater contaminated with barium is of concern because of the potential for humans to ingest such water. Contaminated soil and groundwater also are of concern because individuals may directly become exposed dermally through airborne dusts, through direct contact with contaminated soil from construction, excavation, or recreational activities, and/or through direct contact by showering with contaminated water.

There is little quantitative information regarding the extent of barium absorption following inhalation, oral, or dermal exposure. Available evidence indicates that barium is absorbed to some extent following inhalation, oral, and dermal exposure; however, absorption in some cases is expected to be limited. For example, there is some evidence that gastrointestinal absorption of barium in humans is less than 5-30% of the administered dose. These latter data suggest that although individuals may become exposed orally to high levels of barium, adverse health effects may not necessarily develop because of the limited gastrointestinal absorption. Another important factor affecting the development of adverse health effects in humans is the solubility of the barium compound to which the individual is exposed. Soluble barium compounds would generally be expected to be of greater health concern than insoluble barium compounds because of the greater potential of soluble barium compounds to be absorbed by the body.

The different barium compounds have different solubilities in water and body fluids and therefore they serve as variable sources of the Ba^{2+} ion. The Ba^{2+} ion and the soluble compounds of barium (notably chloride, nitrate, hydroxide) are toxic to humans. The insoluble compounds of barium (notably sulfate and carbonate) are inefficient sources of Ba^{2+} ion because of limited solubility and are therefore generally nontoxic to humans (IL0 1983). The insoluble, nontoxic nature of barium sulfate has made it practical to use this particular barium compound in medical applications such as enema procedures and in x-ray photography of the gastrointestinal tract. Barium provides an opaque contrasting medium when ingested or given by enema prior to x-ray examination. Under these routine medical situations, barium sulfate is generally safe. However, barium sulfate or other insoluble barium compounds

may potentially be toxic when it is introduced into the gastrointestinal tract under conditions where there is colon cancer (Princenthal et al. 1983) or perforations of the gastrointestinal tract and barium is allowed to enter the blood stream.

Barium has been associated with a number of adverse health effects in both humans and experimental animals. Both human and animal evidence suggests that the cardiovascular system may be one of the primary targets of barium toxicity. In addition to cardiovascular effects, exposure of humans and/or animals to barium has been associated with respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, renal, neurological, developmental, and reproductive effects. No data or insufficient data are available to draw conclusions regarding the immunological, genotoxic, or carcinogenic effects of barium. Death has been observed in some individuals following acute oral exposure to high concentrations of barium. The following section evaluates the significance of existing toxicity data on barium with regard to human health.

Death. No studies were available regarding death in humans or animals after inhalation or dermal exposure to barium. However, mortality has been reported to occur in a number of cases where humans have been exposed acutely to barium through accidental or intentional ingestion (Das and Singh 1970; Diengott et al. 1964; McNally 1925; Ogen et al. 1967; Talwar and Sharma 1979). The observations from human case reports are supported by findings from acute studies with rodents that indicate barium is toxic by the oral route (Borzelleca et al. 1988; Tardiff et al. 1980). Reduced lifespan also has been observed in chronic oral studies with mice (Schroeder and Mitchener 1975b). The results from human case studies and animal studies suggest that humans who are exposed orally to high levels of barium may be at increased risk for mortality.

One death in an adult female due to acute intravasation of barium sulfate during a barium enema was found in the literature. Direct entry of barium sulfate into the circulatory system apparently resulted in cardiorespiratory failure (Cove and Snyder 1974). Acute parenteral administration of barium compounds to animals has resulted in death. Rate of administration, total dose, species, and individual differences are all factors affecting the ability of barium and its compounds to cause death. Major symptoms leading to death are hypokalemia (Jalinski et al. 1967; Roza and Berman 1971; Schott and McArdle 1974), muscle paralysis (Roza and Berman 1971; Schott and McArdle 1974), cardiorespiratory failure (Cove and Snyder 1974; Roza and Berman 1971), and convulsions (Segreti et al. 1979; Welch et al. 1983). Parenteral administration is not a normal route of barium exposure in humans and only on the rare occurrence of intravasation during barium enema would it be expected to be a problem. However, many of the symptoms experienced are the same as those experienced by humans and animals exposed to acute doses by inhalation and ingestion.

Systemic Effects

Respiratory Effects. Studies evaluating the respiratory effects of barium following inhalation, oral, and dermal exposure are limited. Benign pneumonoconiosis has been observed in workers exposed occupationally by inhalation to barium (Doig 1976). However, no respiratory effects were observed in another study of workers exposed to barium carbonate dust by inhalation (Essing et al. 1976). There are case reports of individuals who developed respiratory weakness and paralysis following acute ingestion of barium (Das and Singh 1970; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Respiratory effects have not been evaluated in humans following dermal exposure. Accumulation of fluid in the trachea has been noted in acute oral studies with rats (Borzelleca et al. 1988). The results from human case and occupational studies and from acute oral studies with rats suggest that humans who are exposed orally or by inhalation to barium may be at increased risk for minor respiratory effects.

Acute intravasation of barium sulfate into the circulatory system of an adult female patient following a barium enema procedure caused the compound to be deposited in blood vessels throughout the body, including the lungs, and resulted in respiratory failure (Cove and Snyder 1974). Acute parenteral administration of barium compounds to animals has been shown to result in paralysis of the respiratory muscles (Roza and Berman 1971). Similar respiratory paralysis is frequently encountered in cases of acute exposure in humans and animals by ingestion or inhalation. Intratracheal administration of barium sulfate into rat lungs produced a mild inflammatory reaction (Huston et al. 1952). Barium sulfate could not be removed by either polymorphonuclear leukocytes or monocytes. A tissue reaction followed; however, no fibrosis was observed. Since this mode of entry is similar to inhalation, these results may be significant for cases of inhalation exposure.

Cardiovascular Effects. No reliable information is available regarding cardiovascular effects in humans or animals for inhalation or dermal exposure. However, case reports of humans exposed orally by acute ingestion and results of acute, intermediate, and chronic oral studies with experimental animals indicate that barium induces a number of cardiovascular effects. These effects include increased blood pressure, changes in heart rhythm, myocardial damage, and changes in heart physiology and metabolism (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Kopp et al. 1985; Lewi and Bar-Khayim 1964; McNally 1925; Perry et al. 1983, 1985, 1989; Talwar and Sharma 1979; Wetherill et al. 1981). The results from this study suggest that humans who are exposed orally to barium may be at increased risk for cardiovascular effects.

In addition to cardiovascular effects following oral exposure, cardiovascular effects have been observed in humans following intravasation of barium and in animals following parenteral barium exposure. During a barium

sulfate enema procedure on an adult female, the patient developed cardiorespiratory failure (Cove and Snyder 1974). On necropsy, barium sulfate was found throughout the circulatory system, including the heart. The authors attributed the death of the woman to barium intravasation. In animals, parenteral administration of barium compounds has been shown to cause hypertension and dysrhythmias (Foster et al. 1977; Mattila et al. 1986; Roza and Berman 1971). Although parenteral exposure is not a common exposure route for humans, similar symptoms are observed in cases of acute oral and inhalation exposure in humans and animals.

In vitro research in mammalian systems indicated barium induces both contraction and automaticity in isolated hearts and heart muscles (Delfino et al. 1988; Ehara and Inazawa 1980; Hiraoka et al. 1980; Katzung and Morgenstern 1976; Mascher 1973; Munch et al. 1980; Saeki et al. 1981; Slavicek 1972; Toda 1970). Electrical and mechanical effects caused by barium appear to be primarily calcium dependent, although barium could still induce contractions and pacemaker activity in calcium deficient media (Ebeigbe and Aloamaka 1987; Ehara and Inazawa 1980; Hiraoka et al. 1980; Slavicek 1972; Toda 1970). Barium has also been shown to cause significant alterations of most myocyte components and degeneration of mitochondria and the contractile apparatus (Delfino et al. 1988). Repeated exposures to barium in isolated heart systems resulted in tachycardia (Ebeigbe and Aloamaka 1987). These in vitro findings offer some possible explanations for the heart abnormalities seen in barium toxicity in humans and animals.

Gastrointestinal Effects. Reliable human and animal studies evaluating the gastrointestinal effects of barium following inhalation and dermal exposure were not available. Data from case reports of humans suggest that gastrointestinal hemorrhage and gastrointestinal disturbances, including gastric pain, vomiting, and diarrhea, have been associated with acute oral exposure to barium (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Talwar and Sharma 1979; Wetherill et al. 1981). Inflammation of the intestines has been noted in acute oral studies with rats (Borzelleca et al. 1988). No data were available from intermediate or chronic exposure studies. Results from human case studies and acute studies with rats suggest that humans exposed orally to barium for acute periods may develop gastrointestinal effects.

Two case studies of acute intrusion of barium sulfate into the peritoneal space during barium enema examination of four men showed barium sulfate caused an acute inflammatory tissue response (Kay 1954; Yamamura et al. 1985), and in one case resulted in formation of a fibrous granuloma (Kay 1954). This is an extremely rare mode of entry and not of significant concern for individuals exposed at a hazardous waste site. Increased fluid accumulation in the intestinal lumen of rats was observed after intraperitoneal injection of barium chloride (Hardcastle et al. 1983b, 1985); however, this observation is not significant for individuals exposed at

hazardous waste sites because of the route of exposure and because there has been no documentation of this effect occurring in humans following normal exposure routes.

Limited studies have been done in vitro on mammalian gastrointestinal systems. Generally, they indicated that barium induced intestinal secretion by releasing intracellular calcium, which combined with calmodulin to stimulate the secretory process (Hardcastle et al. 1983a, 1983b, 1985). Barium also increased gastrointestinal tissue sugar accumulation and decreased mucosal to serosal galactose fluxes. The two proposed mechanisms for this are (1) activation of the calcium-calmodulin complex or (2) direct action of barium on smooth muscle tone (Alcalde and Ilundain 1988). The relevance of these effects on the gastrointestinal tract is unknown.

Hematological Effects. No reliable studies were available regarding hematological effects in humans or animals following inhalation or dermal exposure to barium. There is suggestive evidence from case reports that acute inhalation, oral, and dermal exposure of humans is associated with lowered blood potassium levels (Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Shankle and Keane 1988; Stewart and Hummel 1984; Talwar and Sharma 1979; Wetherill et al. 1981). These findings suggest that humans exposed to barium by various routes may be at increased risk for minor hematological effects.

Several studies of animals exposed to barium by parenteral routes indicate that barium decreases in serum potassium (Foster et al. 1977; Jaklinski et al. 1967; Roza and Berman 1971; Schott and McArdle 1974). In one study, dogs intravenously administered barium chloride demonstrated a decrease in serum potassium accompanied by an increase in red blood cell potassium concentration (Roza and Berman 1971). The authors concluded that the observed hypokalemia was due to a shift of potassium from extracellular to intracellular compartments and not to excretion. Additional intravenous studies have linked the observed hypokalemia to muscle paralysis in rats (Schott and McArdle 1974) and cardiac arrhythmias in dogs (Foster et al. 1977). These experiments in animals strongly support the suggestive human case study evidence indicating hypokalemia is an important effect of acute barium toxicity.

Musculoskeletal Effects. No studies were available in humans or animals regarding musculoskeletal effects of barium following dermal exposure. Case reports of humans indicate that acute inhalation and acute oral exposure to barium has been associated with muscle weakness and paralysis (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Shankle and Keane 1988; Wetherill et al. 1981). Occupational exposure has not, however, been found to result in radiologically apparent barium deposits in skeletal muscle or bone (Essing et al. 1976). Very limited animal data are available regarding musculoskeletal effects. No adverse effects on the musculoskeletal

system were reported in an intermediate oral study with rats (Tardiff et al. 1980). The findings from human case reports suggest that humans having acute oral or inhalation exposure to barium may develop musculoskeletal effects.

No data on musculoskeletal involvement in cases of barium exposure by other than oral or inhalation modes have been reported for humans. In animals receiving acute doses of barium compounds parenterally, both muscle twitching and paralysis have been reported. Muscle twitching usually occurred within minutes of injection with flaccid paralysis following (Roza and Berman 1971; Schott and McArdle 1974). Parenteral administration is a very rare route of barium exposure, but once barium has entered the bloodstream and has been systemically distributed, it will have the same effects on the same organ. Similar symptoms are expected to occur in humans acutely exposed to barium via inhalation and oral routes.

Barium induced smooth muscle contractions in a variety of in vitro mammalian systems (Antonio et al. 1973; Breuing et al. 1987; Clement 1981; Ebeigbe and Aloamaka 1987; Ehara and Inazawa 1980; Karaki et al. 1967; Mishra et al. 1988; Munch et al. 1980; Saeki et al. 1981; Saito et al. 1972; Slavicek 1972). Contraction appears to be calcium dependent (Antonio et al. 1973; Breuing et al. 1987; Clement 1981; Karaki et al. 1967; Saito et al. 1972), although the exact mechanism is unknown (Breuing et al. 1987; Clement 1981; Mishra et al. 1988).

Hepatic Effects. No reliable human or animal data were available regarding hepatic effects following inhalation or dermal exposure. Degeneration of the liver following acute oral exposure to barium has been noted in one human case report (McNally 1925). Increased liver/brain weight ratio and darkened liver were observed in rats following acute oral exposure to barium (Borzelleca et al. 1988). Decrease blood urea nitrogen, a potential sign of altered hepatic activity, was also noted in this study (Borzelleca et al. 1988). The available data are too limited to conclusively determine whether or not oral exposure to barium is associated with increased risk of hepatic effects in humans.

Renal Effects. No dermal studies evaluating renal effects in humans or animals were available. Renal failure was reported in one case study of a human exposed by acute inhalation to barium (Shankle and Keane 1988). Case studies of humans developing renal failure, renal insufficiency, and renal degeneration following acute oral barium poisoning have been reported (Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Phelan et al. 1984; Wetherill et al. 1981). Increased kidney/body weight ratio has been observed in rats following acute oral exposure to barium (Borzelleca et al. 1988). Renal effects have not been observed in intermediate or chronic oral studies with rats (Schroeder and Mitchener 1975a; Tardiff et al. 1980). Together, the findings from human case reports and animal studies suggest that individuals exposed to barium by acute inhalation or ingestion may be at increased risk of developing minor renal effects.

One in vitro study on rat renal tissue homogenate showed barium weakly inhibited the sodium-potassium-adenosine triphosphatase enzyme system (Kramer et al. 1986). A second study on mouse kidney tubules showed barium chloride could depolarize the membrane and inhibit potassium transport (Valkl et al. 1987). A similar defect in cell membrane transport in humans could be responsible for the renal involvement observed in some cases of acute barium poisoning.

Dermal/Ocular Effects. Few inhalation or dermal studies evaluating dermal/ocular effects in humans or animals are available. Results of one limited study suggested that barium carbonate was a dermal and ocular irritant when applied to the skin and eye of animals; however, it was not clear whether or not control animals were used (Tarasenko et al. 1977). In studies with Sprague-Dawley rats, both ocular discharge following acute oral exposure (Borzelleca et al. 1988) and nonsignificant increases in retinal dystrophy following intermediate and chronic oral exposure (McCauley et al. 198.5) have been observed. Although the retinal dystrophy was not statistically significant, a dose-related trend was noted in several groups of rats if different duration exposure groups were combined. Both ocular discharge and retinal dystrophy are commonly observed in Sprague-Dawley rats; consequently, these ocular lesions cannot necessarily be attributed to oral barium exposure. Together, these results from animal studies provide unreliable information to draw firm conclusions about dermal/ocular effects in humans following barium exposure.

Other Systemic Effects. Other systemic effects have been observed. Barium sulfate was observed to act as an appendocolith in two cases following barium enema procedures (Palder and Dalessandri 1988). This is a rare occurrence and probably not significant in cases of human barium toxicity. Intravenous injection of barium sulfate into pigs increased calcitonin secretion from the thyroid (Pento 1979). This is probably not a significant effect for humans since intravenous exposure is not a common route and the dose required was so high (1.7 mg/kg/minute for 20 minutes) it caused cardiotoxicity.

Limited data are available on In vitro effects of barium on the endocrine system. Studies done with isplated pancreatic islet cells from mice show barium is transported across the cell membrane and incorporated into organelles, especially the mitochondria and secretory granules (Berggren et al. 1983). Barium was found to increase cytoplasmic calcium: consequently, the insulin-releasing action of barium may be mediated by calcium. Barium has also been found capable of stimulating the calcitonin secretion system of the thyroid in pigs (Pento 1979).

Immunological Effects. No information was available regarding immunotoxicity in humans following exposure to barium. Acute oral exposure of rats to barium failed to induce changes in thymus weight or gross or

microscopic lesions of the thymus (Borzelleca et al. 1988). Information from this study is too limited to draw any conclusions regarding relevance to human health.

An in vitro immunological study indicated that barium sulfate in low doses for relatively short periods posed no serious toxic hazard to phagocytic cells (Rae 1977).

Neurological Effects. No data were available regarding neurological effects in humans and/or animals following dermal exposure. One case study of a human accidentally exposed by acute inhalation to barium noted the absence of deep tendon reflexes (Shankle and Keane 1988). Case studies of humans having acute oral exposure to barium have reported such effects as numbness and tingling of the mouth and neck, partial and complete paralysis, and brain congestion and edema (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). Acute and intermediate oral exposure of rats to barium has not been associated with changes in brain weight or with gross or microscopic changes of the brain (Borzelleca et al. 1988; Tardiff et al. 1980). Based on the limited, but suggestive evidence from human case studies, there is the potential that individuals exposed by acute inhalation or acute oral exposure to barium may be at increased risk of developing neurological effects.

There are no cases of neurological effects in humans following parenteral exposure to barium compounds. In a few animal studies where barium chloride was injected intracerebroventricularly, insensitivity to pain occurred within minutes (Welch et al. 1983) followed by fatal convulsions if the dose was sufficient (Segreti et al. 1979; Welch et al. 1983). The significance of these data is difficult to assess since this unusual mode of entry would not occur in humans, and could be partially responsible for the rapid and extreme effects. Intraperitoneal injection of barium sulfate into mice produced an immediate increase in electroshock sensitivity followed by a decrease in sensitivity 24 hours later (Peyton and Borowitz 1978). These results are also difficult to assess in terms of effects observed in cases of human exposure, but suggest that barium in sufficient amounts may potentially influence brain function.

In most in vitro studies of nerve fibers, barium prolonged the action potential and caused rhythmic discharges (de No and Feng 1946; Greengard and Straub 1959). Barium released catecholamines in the absence of calcium both after nerve stimulation and in the absence of stimulation (Boullin 1965, 1967; Douglas and Rubin 1964a; Nakazato and Onoda 1980; Shanbaky et al. 1978). Barium also inhibited potassium flux in glial cells (Walz et al. 1984). These in vitro effects provide clues to the possible mechanism by which barium induces toxic effects on the cardiovascular and musculoskeletal systems. Barium had only a weak effect in blocking activation of spinal cord neurons by

excitatory amino acids (Ault et al. 1980). Barium was also taken up by mitochondria in bovine adrenal medulla (Shanbaky et al. 1982). These organelles therefore maybe more susceptible to the toxic effects of barium.

Developmental Effects. Little information is available regarding developmental effects in humans and/or animals following inhalation, oral, or dermal exposure to barium. One study reported reduced survival, underdevelopment, lowered weight, decreased lability of the peripheral nervous system, and various blood disorders in offspring of female rats exposed by intermediate inhalation to barium (Tarasenko et al. 1977). The same study also reportedly observed increased mortality, increased leukocyte count, disturbances in liver function, and increased urinary excretion of hippuric acid in offspring of female rats treated orally with barium during conception and pregnancy (Tarasenko et al. 1977). These studies are inadequate for evaluating the developmental effects of barium because of a number of significant study limitations (see Sections 2.2.1.2 and 2.2.2.5). In view of the major study limitations, and until verified by further tests, results from these studies should be regarded as providing only preliminary and/or suggestive evidence that inhalation and oral exposure to barium is potentially associated with adverse developmental effects.

Reproductive Effects. No studies were available regarding reproductive effects in humans following inhalation, oral, or dermal exposure. Disturbances in spermatogenesis, shortened estrous cycle, and alterations in the morphological structure of the ovaries and testes were reportedly observed in intermediate exposure experiments in which rats were treated by inhalation with barium carbonate dust (Tarasenko et al. 1977). However, these experiments suffered from a number of major limitations (see Section 2.2.1.2). Acute oral exposure of rats to barium has been associated with decreased ovary/brain weight ratio and decreased ovary weight (Borzelleca et al. 1988). These latter animal findings suggest that humans exposed orally to barium may be at increased risk of reproductive effects.

Genotoxic Effects. No data on in vivo studies of barium genotoxicity were available. In vitro studies were limited and primarily involve prokaryotic test systems, Tests of the fidelity of DNA synthesis using an avian myeloblastosis virus (AMV) DNA polymerase system showed that neither barium acetate nor barium chloride affect the accuracy of DNA replication (Sirover and Loeb 1976a; Sirover and Loeb 1976b). Barium chloride produced negative test results for its ability to inhibit growth in wild and recombination deficient strains of Bacillus subtilis. These results indicate that barium chloride is not mutagenic (Nishioka 1975). However, studies with a DNA polymerase I system from Micrococcus luteus, demonstrated that concentrations of barium ion less than or equal to 0.1 mM stimulated DNA polymerase activity while concentrations greater than this inhibited polymerase activity (Korman et al. 1978). The significance of the inhibitory and stimulatory effects has not been determined. Results from an experiment

designed to test the effect of barium chloride on sporulation frequency, recombination frequency, and meiotic failures in Saccharomyces cerevisiae demonstrated a definite inhibition of sporulation. Effects on recombination frequency and meiotic failures were ambiguous. Barium chloride may have caused a marginal increase in recombination frequencv and information of diploid clones (Sora et al. 1986), but the data are inconclusive. The data available to date are insufficient to support a conclusive statement regarding the genotoxicity of barium and barium compounds.

Cancer. No adequate human studies were available that evaluated the carcinogenic potential of barium. Two chronic oral studies were available that examined the incidence of tumors in rats and mice exposed to barium acetate in drinking water for lifetime (Schroeder and Mitchener 1975a, 1975b). Although results of these oral studies were negative for carcinogenicity, they were inadequate for evaluating carcinogenic effects because insufficient numbers of animals were used, it was not determined whether or not a maximum tolerated dose was achieved, a complete histological examination was not performed, and only one exposure dose was evaluated. Precancerous lesions (dysplasia) were reported in one study in which a woman was treated on the cervix with a barium chloride solution; however, the relevance of this limited observation cannot be determined because only one subject was treated and because the vehicle solution was not specified (Ayre 1966). Results of one skin-painting study with mice suggest that barium hydroxide extract derived from tobacco leaf acted as a tumor-promoting agent; however, it cannot be determined whether or not this apparent positive tumorigenic response was due to barium hydroxide or some other component of the tobacco leaf extract (Van Duuren et al. 1968). Barium has not been evaluated by EPA for human carcinogenic potential (IRIS 1991).

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of

exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to barium are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by barium are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UN-USUALLY SUSCEPTIBLE."

At present, there are no‘well-established biomarkers of exposure and effect for barium. Data suggesting possible biomarkers are presented below.

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Barium

Barium can be measured in bone, blood, urine, and feces. It has been shown to be sequestered in bone and teeth and excreted in feces and urine. Background levels of barium in bone are approximately 2 μg/g wet weight (ICRP 1974; Scroeder et al. 1972). Background levels of barium in blood, urine, and feces will vary with daily intake of barium. However, the following levels have been reported: bone, 2 ppm (ICRP 1974; Scroeder et al. 1972); feces, 690-1,215 μg/day (ICRP 1974; Scroeder et al. 1972; Tipton et al, 1969); and urine, 17-50 μg/day (ICRP 1974; Scroeder et al. 1972; Tipton et al. 1969). There are no data correlating bone, blood, urine, or feces levels of barium with specific exposure levels. For more detailed information on the toxicokinetics of barium, see Section 2.3.

Hypokalemia and hypertension are effects usually found in cases of acute and intermediate exposures to relatively high doses of barium. While it is reasonable to expect the dose level to influence the presence of these effects, there are no data supporting a correlation between dose level and

either appearance of or degree of hypokalemia and hypertension. Observation of hypokalemia and hypertension together is indicative of barium exposure, however, other toxicants and disease states can produce these effects.

2.5.2 Biomarkers Used to Characterize Effects Caused by Barium

The organs most sensitive to the toxic effects of barium are the organs of the cardiovascular and gastrointestinal systems, muscles, and nerves. Gastrointestinal disturbances are usually the first symptoms of acute barium exposure. Hypokalemia, hypertension, and abnormalities in heart rhythm frequently occur. General muscle weakness is a frequent symptom, sometimes followed by paralysis. Nerve conduction is often affected, resulting in numbness and tingling of the mouth, neck and extremities. Loss of deep tendon reflexes may also occur. Not all symptoms appear in every case of acute barium poisoning. The presence of other toxicants and disease states may also cause these effects. More information on the specific effects of barium toxicity can be found in Section 2.2.

2.6 INTERACTIONS WITH OTHER CHEMICALS

There are no data regarding the interaction between barium and various chemicals potentially found at hazardous waste sites. However, there are data that suggest that barium may interact with other cations and certain prescription drugs. Drug interactions are of relevance because individuals exposed to barium by living or working near hazardous waste sites contaminated with this substance may also be taking prescription drugs.

The cations potassium, calcium, and magnesium also interact with barium. Barium exposure, for example, may cause a buildup of potassium inside the cell resulting in extracellular hypokalemia which is believed to mediate bariuminduced paralysis. In fact, potassium is a powerful antagonist of the cardiotoxic and paralyzing effects of barium in animals (Foster et al. 1977; Jaklinski et al. 1967; Roza and Berman 1971; Schott and McArdle 1974) and is used as an antidote in cases of acute barium poisoning. Calcium and magnesium suppress uptake of barium in vitro in pancreatic islets. Conversely, barium, in low concentrations, stimulate calcium uptake in these cells. Although the data are insufficient to determine the significance of these findings to human health effects, displacement of calcium may be the mechanism by which barium stimulates insulin release (Berggren et al. 1983).

Among the drugs which are known to interact with barium, the barbiturates sodium pentobarbital and phenobarbital were found to have an increased depressive effect on the hearts of rats exposed to barium (Kopp et al. 1985; Perry et al. 1983, 1989). This hypersensitivity of the cardiovascular system to anesthesia was not observed in similarly treated animals that were anesthetized with xylazine plus ketamine. Results of the study indicated that the hypersensitivity was specific .to the barbiturates and not a generalized effect of anesthesia (Kopp et al. 1985).

Other medically prescribed drugs interact with barium. Experiments with mice indicated that atropine significantly antagonized antinociception and death induced by intracerebroventricular injection of barium chloride (Segreti et al. 1979; Welch et al. 1983). These same studies also found that naloxone, a narcotic antagonist, inhibited the lethal toxicity of barium (Segreti et al. 1979; Welch et al. 1983). Propranolol had no effect 'on barium-induced paralysis in rats (Schott and McArdle 1974). Verapamil rapidly abolished cardiac dysrhythmias in rabbits injected with barium chloride (Mattila et al. 1986). In the same study, pretreatment with the tricyclic antidepressant, doxepin, was found to offer some protection against barium-induced dysrhythmias (Mattila et al. 1986). Cuabain which is an inhibitor of Na^+-K^+ ATPase, while not widely prescribed, has been shown to rapidly reverse the paralyzing effects of barium. it has been hypothesized that ouabain works by reducing barium-induced hypokalemia thereby allowing some intracellular potassium to escape. However, this hypothesis has not yet been proved or disproved because of the complexity of the mechanism involved (Schott and McArdle 1974).

Other substances can affect barium pharmacokinetics. One study showed that sodium alginate could reduce retention of orally administered barium, possibly by inhibiting reabsorption in the gut (Sutton et al. 1972). This could be useful in treating cases of acute barium ingestion. Lysine and lactose increase absorption of barium and could increase the toxic effects of oral exposure (Lengemann 1959).

A human study involving one adult female was performed by applying barium chloride, alone and in combination, with dimethyl sulfoxide to the cervical epithelium. Dimethyl sulfoxide significantly enhanced the ability of barium chloride to induce dysplasia with unusual cell formation in the cervical epithelium (Ayre 1966). The significance of this is difficult to determine since there was only one subject, there were no controls, and few details of the experiment were provided.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

The limited data available suggest that certain subgroups of the population may be more susceptible to barium exposure than the general population. These include people with cardiovascular problems, those taking certain prescription drugs, children, pregnant women, smokers, and people with lung disease.

A consistent toxic effect of barium in humans and animals is increased blood pressure. Therefore, humans with hypertension could be at increased risk from either chronic, intermediate, or acute barium exposure. In addition, the cardiotoxic effects of barium exposure could increase the risk for those individuals suffering from other heart problems.

Barbiturates have been shown to have an enhanced depressant effect on the heart in barium-exposed animals (Kopp et al. 1985; Ferry et al. 1983, 1989). Individuals on this type of medication may experience an increased risk of heart problems on exposure to barium.

Children may be at an increased risk since animal studies have demonstrated a higher absorption rate among younger animals than older animals (Taylor et al. 1962). However, a study of an epidemic of oral barium poisoning in Poland indicated that children did not react as adversely as adults even when they had ingested the same amount or more of barium (Lewi and Bar-Khayim 1964; Ogen et al. 1967).

One study showed an increase in barium absorption in the presence of lysine and lactose and could indicate an increased risk in individuals who drink large quantities of milk (Lengemann 1959). These would include young children and pregnant women.

People who smoke and those who have a history of lung disease may be at an increased risk of exposure by inhalation. Studies show that inhalation of dust from barium salts produces a mild, but lengthy, inflammatory response in the lungs of rats (Huston et al. 1952). A benign pneumoconiosis has been noted in cases of chronic, low-level exposure in humans (Doig 1976). Smoking and lung diseases may increase the intensity of this response in affected individuals.

Since barium toxicity has been repeatedly demonstrated to significantly decrease serum potassium in both humans and animals (Foster et al. 1977; Gould et al. 1973; Phelan et al. 1984; Roza and Berman 1971), individuals taking diuretics may have a more severe hypokalemic reaction to barium toxicity.

2.6 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to barium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to barium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

General recommendations for reducing absorption of barium following exposure have included removing the exposed individual from the contaminated area and removing contaminated clothing, followed by washing with mild soap and water. If the eyes and skin were exposed, they are flushed with water. Lavage or emesis has also been suggested; however, high concentrations of barium cause nausea and emesis should not be induced in cases where substantial vomiting has already occurred (Haddad and Winchester 1990). Furthermore, there is a risk of aspiration of vomitus during emesis. Administration of soluble sulfates orally will also limit absorption of barium

by causing precipitation of an insoluble form of barium (barium sulfate) (Dreisbach and Robertson 1987; Haddad and Winchester 1988). Intravenous administration of sulfate salts should be avoided because barium precipitate in the kidneys will cause renal failure (Dreisbach and Robertson 1987). Removal of barium from the bloodstream may be facilitated by infusing with saline and inducing saline diuresis (Dreisbach and Robertson 1987).

Hypokalemia is commonly seen in cases of acute barium toxicity and may be responsible for some of the symptoms of barium poisoning (Proctor et al. 1988). Plasma potassium should be monitored and hypokalemia may be relieved by intravenous infusion of potassium (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988).

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of barium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of barium.

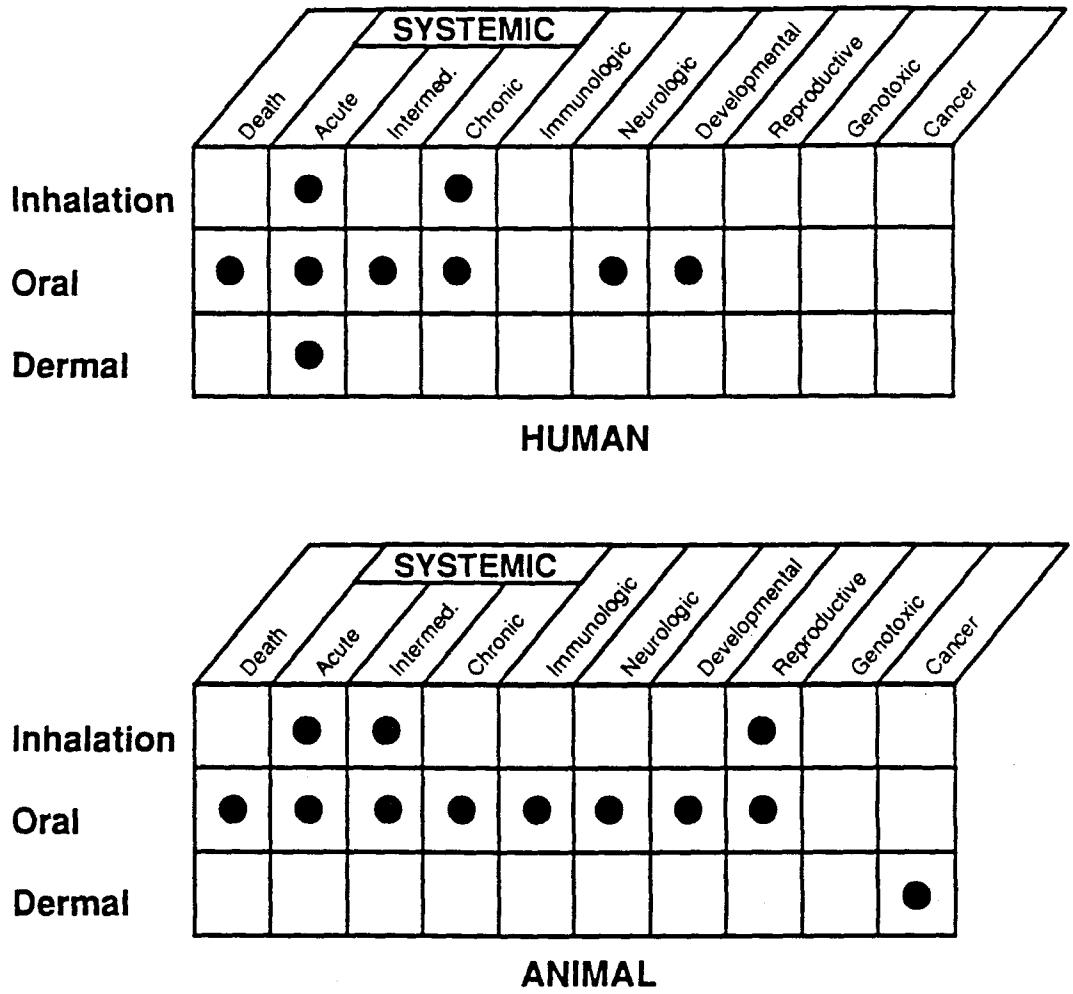
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Barium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to barium are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of barium. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

There is little information regarding health effects in humans following inhalation, oral, or dermal exposure to barium (Figure 2-2). Inhalation studies are limited to several case reports of individuals exposed acutely or. chronically through occupational exposure (Doig 1976; Essing et al. 1976; Seaton et al. 1986; Shankle and Keane 1988). Oral studies are limited to a number of case reports of individuals exposed through acute ingestion (Das and

FIGURE 2-2. Existing Information on Health Effects of Barium



Singh 1970; Diengott et al. 1964; McNally 1925; Ogen et al. 1967; Talwar and Sharma 1979), a single intermediate-duration experimental study (Wones et al. 1990), and several human epidemiological studies or statistical studies examining mortality and morbidity rates in communities having exposure to barium through drinking water supplies (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974). Dermal studies are limited to one case report of an exposed individual (Stewart and Hummel 1984).

The majority of studies conducted on animals have been oral exposure studies (Figure 2-2). These oral studies have focused on examining mortality or various systemic effects following acute (Borzelleca et al. 1988; Boyd and Abel 1966; Tardiff et al. 1980), intermediate (McCauley et al. 1985; Perry et al. 1983, 1985, 1989; Tarasenko et al. 1977; Tardiff et al. 1980), and chronic exposure (Kopp et al. 1985; McCauley et al. 1985; Perry et al. 1983, 1985, 1989; Schroeder and Mitchener 1975a, 1975b). Available inhalation studies with experimental animals (Hicks et al. 1986; Tarasenko et al. 1977) can only suggest information on the health effects of barium because these studies have a number of limitations and deficiencies. Dermal studies with experimental animals are limited to one skin irritation study (Tarasenko et al. 1977) and one study evaluating the tumor-promoting activity of barium (Van Duuren et al. 1968).

2.9.2 Data Needs

Acute-Duration Exposure. The majority of experimental studies involving acute.exposure to barium chloride have focused on oral exposure of rats (Borzelleca et al. 1988; Tardiff et al. 1980). These studies have determined acute oral LD_{50} values, as well as evaluated systemic effects. Systemic effects were evaluated primarily by monitoring body weights, selected organ weights, and various hematological and blood chemistry parameters, and by performing gross and microscopic examinations of selected organs and tissues. These studies have provided evidence that barium chloride is lethal by oral ingestion (LD_{50}s range from 132 to 277 mg/kg). The study by Borzelleca et al. (1988) has also provided evidence that acute oral barium exposure is associated with reduced blood urea nitrogen, inflammation of the intestines, accumulation of fluid in the trachea, decreased liver/brain weight ratio, darkened liver, increased kidney/body weight ratio, decreased body weight, decreased ovary weight, and decreased ovaries/brain weight ratio. This study has also provided information as to the barium levels inducing these effects in experimental animals. In the only available acute inhalation study, limited evidence was provided suggesting that barium exposure is potentially associated in rats with increased blood pressure and bronchoconstriction (Hicks et al. 1986). However, this inhalation study was limited in that no controls were used, Limited acute testing of experimental animals also has provided suggestive evidence that barium carbonate is both a dermal and ocular irritant (Tarasenko et al. 1977). Given the available data from acute

exposure studies, additional acute oral studies that focus on mechanisms of toxicity useful.and that further establish and/or refine effect thresholds would be Additional studies of barium following inhalation and dermal exposure would be useful because the potential adverse effects of these two routes have not been thoroughly studied. This information is important because populations exposed to barium from hazardous waste sites may be exposed for a similar duration.

Intermediate-Duration Exposure. The majority of available intermediate-duration studies have focused on oral exposure of experimental animals (McCauley et al. 1985; Perry et al. 1983, 1985, 1989; Tarasenko et al. 1977; Tardiff et al. 1980). Several intermediate oral studies with rats have evaluated mortality and systemic effects (McCauley et al. 1985; Tardiff et al. 1980). Systemic effects were evaluated by monitoring body weight, selected organ weights, food consumption, clinical signs of toxicity, and a variety of hematological and blood chemistry parameters, and by performing gross and microscopic examinations on a wide variety of organs and tissues. Generally, no toxicologically significant adverse effects were noted in any of these parameters. Other intermediate oral studies (Perry et al. 1983, 1985, 1989) have provided evidence that barium induces increased blood pressure. The mechanism of action of this cardiovascular effect has not been established. Various renal lesions have been observed in two intermediate oral experiments with rats (McCauley et al. 1985); however, these studies were of limited value because control rats were not used. Nonsignificant increases in retinal dystrophy have been observed in several intermediate oral experiments with rats (McCauley et al. 1985). It is particularly noteworthy that when these various experiments are combined, a dose-related increase in this ocular lesion is observed. No intermediate dermal studies were available. In the only available intermediate inhalation study (Tarasenko et al. 1977), barium exposure was associated in rats with decreased body weight, altered hematological and blood chemistry parameters, impaired hepatic detoxifying function, and pulmonary lesions. However, this study was of limited value because the number of rats evaluated was not specified. Given the available data, additional intermediate oral studies focusing on the association between barium exposure and hypertension in animals ingesting a normal diet, the mechanism by which barium increases blood pressure, and the potential of barium to induce renal lesions, ocular lesions and various cardiovascular effects would be useful. Because the potential adverse effects of barium following inhalation exposure have not been well characterized and dermal exposure have not been studied, additional intermediate-duration exposure studies involving these two routes of exposure would also be useful. This information is important because there are populations surrounding hazardous waste sites that may be exposed to barium for an intermediate duration.

Chronic-Duration Exposure and Cancer. Chronic studies in which rats and mice were exposed to barium in drinking water for lifetime have evaluated both mortality and systemic effects (Schroeder and Mitchener 1975a, 1975b).

Reduced lifespan but no toxicologically significant systemic effects were observed. Systemic effects were evaluated primarily by monitoring body weight and selected organ weights, and by examining selected organs both grossly and microscopically. Tests for organ function and complete histological examinations were not performed. Further, the fact that no systemic effects were observed may be due to the fact that a single relatively low exposure dose was provided. Another chronic drinking water study with rats provided information on the effects of barium on blood pressure and heart physiology and metabolism (Kopp et al. 1985; Perry et al. 1983, 1985, 1989). Both increased blood pressure and myocardial pathophysiologic and metabolic changes were observed in this chronic study; however, the mechanism of action of barium in inducing these cardiovascular effects was not determined. Therefore. additional chronic studies focusing on organ function, histopathological examination of a wider variety of organs and tissues? multiple exposure doses including a maximum tolerated dose, the association between exposure and cardiovascular effects, and mechanism of action in inducing cardiovascular effects would be useful. In all of these studies, it is important to determine whether the divalent cation Ba+2 is responsible for the toxic effects, or if they are caused by the associated anion.

Another consideration for estimating the toxicity of barium, as well *as* other compounds, is that the toxicity may well be altered by interactions with other toxicants. Specifically, barium would be expected to have reciprocal interactions with other trace metals found in the environment and in human tissues (Berggren et al. 1983; Foster et al. 1977; Jaklinski et al. 1967; Roza and Berman 1971; Schott and McArdle 1974). Considerations of these interactions should be made when designing future tests of barium and other compounds.

EPA and IARC have not evaluated barium for human carcinogenic potential. NTP (1990) is in the process of conducting carcinogenicity bioassays with rats and mice (see Section 2.9.3) on barium chloride. No significant differences in tumor incidence between controls and treated rats and mice have been observed in two published chronic oral studies (Schroeder and Mitchener 1975a, 1975b); however, these two studies were not necessarily designed as carcinogenicity bioassays because maximum tolerated doses were not used, single exposure doses were used, complete histological examinations were not performed, the number of animals was too small for oncogenicity testing, and/or the exposure was less than lifetime. One long-term skin-painting study involving dermal exposure of mice to barium hydroxide extract derived from tobacco leaf provided evidence suggesting that this extract may act as a tumor-promoting agent when applied with a tumor initiating agent (Van Duuren et al. 1968); however, it cannot be determined if this tumor-promoting activity was due to barium hydroxide or some other component of the tobacco leaf extract. There also was one case study of a woman who developed dysplasia of the cervix, a potential precancerous lesion, following cervical treatment with a barium chloride solution (Ayre 1966). Given the available information, lifetime studies in which multiple exposure doses are used

(including a maximum tolerated dose) and complete histopathological examinations are performed would provide useful information on the potential carcinogenic effects of barium. A dermal tumor promotion/tumor initiation study evaluating barium hydroxide and other barium compounds would be useful to clear up concerns as to whether or not barium hydroxide is a tumor-promoting agent.

Genotoxicity. The genotoxicity of barium has not been well characterized. The available data relating to the genotoxic effects of barium are derived from in vitro studies only (Korman et al. 1978; Nishioka 1975; Sirover and Loeb 1976a, 1976b; Sora et al. 1986); there were no available data regarding the genotoxicity of barium in vivo. A single recombination assay in which Bacillus subtilis was exposed to barium was negative for mutagenicity (Nishioka 1975). Results of a test evaluating the fidelity of DNA synthesis in an avian myeloblastosis virus DNA polymerase system indicates that barium did not affect the accuracy of DNA replication (Sirover and Loeb 1976a, 1976b). Results of a study with Micrococcus luteus suggested that DNA polymerase activity was stimulated and inhibited at low and high barium concentrations, respectively (Korman et al. 1978). In a study with Saccharomyces cerevisiae, inhibition of sporulation and marginal increases in recombination frequency and diploid clones were observed following barium treatment (Sora et al. 1986). Additional studies evaluating the genotoxic effects of barium in a variety of in vivo and in vitro systems would be useful because there is limited evidence suggesting barium may affect DNA polymerase activity in bacteria and sporulation, meiotic failures, and recombination frequency in yeast. The limited genotoxicity database for barium supports the need for additional genotoxic studies.

Reproductive Toxicity. The reproductive effects of barium have not been thoroughly studied. There are no studies regarding reproductive effects in humans following barium exposure. However, two animal studies have provided limited information suggesting that humans exposed to barium may be at increased risk for developing reproductive effects (Borzelleca et al. 1988; Tarasenko et al. 1977). Decreased ovary weight and decreased ovary/brain weight ratio have been noted in rats following acute oral exposure to barium (Borzelleca et al. 1988). Intermediate inhalation exposure to barium has been associated with disturbances in spermatogenesis, shortened estrous cycle, and alterations in the morphological structure of the ovaries and testes in rats (Tarasenko et al. 1977). Since limited animal evidence suggests a potential for adverse reproductive effects, epidemiological or occupational studies with humans and/or additional experimental studies with animals would be useful to fully characterize the reproductive toxicity of barium. Experimental animal studies evaluating a wide variety of reproductive parameters through multigenerations would be particularly useful because of the limited number of parameters evaluated in the available single-generation studies.

Developmental Toxicity. The developmental effects of barium have not been studied extensively in either humans or animals. One limited statistical study evaluated the degree of correlation between barium concentrations in drinking water and human congenital malformation rates of the central nervous system (Morton et al. 1976). Results of the study indicated there was a negative statistical correlation between these parameters. However, another limited report provided suggestive evidence that exposure to barium may potentially be associated with adverse developmental effects (Tarasenko et al. 1977). Reduced survival, underdevelopment, lowered body weight, decreased lability of the peripheral nervous system, and various blood disorders were reportedly noted in the offspring of rats following inhalation to barium for an intermediate exposure period. In the same report, increased mortality, increased leukocyte count, disturbances in liver function, and increased urinary excretion of hippuric acid were reportedly noted in the offspring of rats treated orally to barium during conception and pregnancy. Epidemiological or occupational studies with humans and/or additional experimental studies with animals would be useful to better characterize the potential developmental and teratogenic effects of barium since the evidence of one animal study suggests that barium exposure may be associated with developmental toxicity.

Immunotoxicity. The effect of barium on the immune system has not been well studied. No studies were available regarding immunological effects in humans or animals following inhalation or dermal exposure to barium. Data regarding immunological effects following oral exposure are limited to two investigations with rats (Borzelleca et al. 1988; McCauley et al. 1985). Results of these studies suggested that acute, intermediate, and chronic oral exposure to barium was not associated with any changes in thymus weight or with any gross or microscopic lesions of the thymus or lymph nodes. Additional studies evaluating a variety of immunological parameters following various routes of barium exposure would be useful because of the limited nature of the immunotoxicity database for barium.

Neurotoxicity. Data regarding the neurological effects of barium are derived primarily from case studies of exposed humans. One case study of a human provided information suggesting that acute inhalation exposure to barium may be associated with absence of deep tendon reflexes (Shankle and Keane 1988). Numerous other case studies of humans has provided information suggesting that acute oral exposure to barium may be associated with numbness and tingling of the mouth, partial or complete paralysis, and brain congestion and edema (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981). However, acute and intermediate oral exposure of rats to barium has not been associated with changes in brain weight or gross or microscopic lesions of the brain (Borzelleca et al. 1968; Tardiff et al. 1980). No data were available regarding neurological effects in humans and/or animals following dermal exposure. Based on the suggestive

evidence from human case studies, there is the potential that individuals exposed to barium at hazards waste sites may be at increased risk for developing neurological effects. Because of this potential for adverse neurological effects and because the majority of the neurotoxicity database consists primarily of uncontrolled human case studies involving acute oral exposure, additional neurotoxicity data derived from controlled experimental studies and involving various routes of exposure and exposure periods would be useful.

Epidemiological and Human Dosimetry Studies. A limited number of epidemiological and human dosimetry studies evaluating the health effects of barium are available (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981; Elwood et al. 1974; Schroeder and Kraemer 1974; Wones et al. 1990). However, all of the available human studies on barium have limitations and/or confounding variables that make it difficult to draw firm conclusions regarding the health effects of barium (see Sections 2.2.2.1 and 2.2.2.2 for discussions on the specific limitations associated with available epidemiological and human dosimetry studies). Two epidemiological studies evaluated mortality and morbidity rates in communities having elevated barium concentrations in drinking water and communities having little or no barium in drinking water (Brenniman and Levy 1985; Brenniman et al. 1979a, 1979b, 1981). Results suggested that relative to low-barium communities, elevated-barium communities had significantly higher mortality rates for all cardiovascular disease, heart disease, arteriosclerosis, and for all causes. No differences between these types of communities were observed with respect to blood pressure, hypertension, stroke, or electrocardiograms. Two statistical studies found negative correlations between barium concentrations in drinking water and rates of cardiovascular mortality and total mortality (Elwood et al. 1974; Schroeder and Kraemer 1974). Results of one human dosimetry study involving a small number of subjects suggested that intermediate exposure to barium in drinking water was not associated with clinically significant changes in blood pressure, electrocardiograms, urinalyses, or hematological parameters (Wones et al. 1990). It is noteworthy that the available epidemiological and human dosimetry studies provide suggestive evidence that barium has no effect on blood pressure. In contrast, results of case studies of humans having acute ingestion exposure (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Wetherill et al. 1981) and experimental studies with animals having intermediate and chronic oral exposure (Perry et al. 1983, 1985, 1989) indicate that barium induces hypertension and increased blood pressure. Therefore, additional epidemiological and/or human dosimetry studies would be useful to determine the effects of barium on blood pressure and other cardiovascular parameters. However, these additional studies may only be useful to the extent that they can control confounding variables and limit study deficiencies that are problematic in currently available studies. Since there are no data or very limited human data regarding the developmental, reproductive, immunotoxic, neurotoxic, and carcinogenic effects

of barium, well-conducted epidemiological studies evaluating these health effects would be useful.

Biomarkers of Exposure and Effect. There are no established biomarkers of exposure for barium. Analytical methods exist for measuring barium in blood, urine, feces, and biological tissues (Mauras and Allain 1979; Schramel 1988; Shiraishi et al. 1987); however, there are no data correlating levels of barium in these tissues and fluids with exposure.

Symptoms of barium toxicity, such as hypokalemia (Diengott *et* al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Phelan et al. 1984; Shankle and Keane 1988; Stewart and Hummel 1984; Talwar and Sharma 1979; Wetherill et al. 1981) hypertension (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Wetherill et al. 1981), and heart (Lewi and Bar-Khayim 1964; McNally 1925; Talwar and Sharma 1979), muscle (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; McNally 1925; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981), and nerve effects (Das and Singh 1970; Diengott et al. 1964; Gould et al. 1973; Lewi and Bar-Khayim 1964; Morton 1945; Ogen et al. 1967; Phelan et al. 1984; Wetherill et al. 1981), are well documented. However, there are no quantitative studies correlating these effects with dose. For purposes of facilitating medical surveillance, studies to determine useful biomarkers of exposure and effect for barium would be useful.

Absorption, Distribution, Metabolism, and Excretion. The database *on* absorption, distribution, metabolism, and excretion of barium is limited. Existing studies indicate that barium is absorbed more efficiently from the respiratory tract (Cuddihy and Ozog 1973b) than from the digestive system (ICRP 1973; Tipton et al. 1969), primarily deposited in the bones and teeth (Bauer et al. 1957; Cuddihy and Griffith 1972; Losee et al. 1974; Miller et al. 1985; Moloukhia and Ahmed 1979; Sowden 1958; Sowden and Pirie 1958; Sowden and Stitch 1957), and excreted mostly in feces and urine (Cuddihy and Griffith 1972; Tipton et al. 1966). Deposition in bones and teeth and excretion in feces and urine appear to be independent of the route of exposure. Essentially no data exist on dermal absorption, distribution, or excretion; however, this route is not considered to be a significant source of exposure to barium. Because barium is an element, it is not metabolized. No significant data exist on the metabolism of barium compounds in the body. Additional studies evaluating the binding and/or complexing of barium and barium compounds with biological macromolecules or organic molecules in the body would be useful. Studies quantifying the extent of absorption following inhalation, oral, and dermal exposure also would be useful because of limited absorption data.

Comparative Toxicokinetics. Based on available data, there do not appear to be significant differences in the toxicokinetics of barium between species (Chou and Chin 1943; Cuddihy and Griffith 1972; McCauley and

Washington 1983). However, there are not enough similar studies on different species to determine this with certainty. Studies on different species would increase confidence in the reliability of the existing database.

Mitigation of Effects. Methods have been reported for limiting oral and dermal absorption of barium compounds (Bronstein and Currance 1988; Dreisbach and Robertson 1987; Haddad and Winchester 1990) and for counteracting the hypokalemia that is produced by barium in acute high-level exposure situations (Dreisbach and Robertson 1987; Haddad and Winchester 1990; Proctor et al. 1988). Contradictions exist in the literature regarding the efficacy or desirability of administering emetics (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Additional studies clarifying this issue would be helpful. Also, studies directed at finding a more efficient way to remove barium from the body would be useful. It is unclear whether mechanisms other than hypokalemia contribute to the toxic effects produced in acute high-level exposure situations. Additional information on the mechanisms responsible for the toxic effects of barium could aid in the development of effective treatments. Magnesium has been reported to antagonize the neuromuscular effects (Dreisbach and Robertson 1987). Additional studies examining the efficacy of administering soluble magnesium salts to antagonize the effects of barium would also be helpful. No information was located on treatment strategies for long-term low-level exposures. Research on procedures for mitigating such chronic exposure situations would be helpful.

2.9.3 On-going Studies

A 2-year lifetime study of barium chloride in drinking water was conducted in rats and mice by the National Toxicology Program. The study was completed in the 1987 fiscal year, however, the histopathological section is still in progress (NTP 1990).

One on-going study regarding health effects of barium was reported in the FEDRIP (1989) database. An epidemiological study is presently being conducted by L. Frohman. The relationship between barium in drinking water and the cardiovascular risk effects to humans is being assessed. No other information was obtained.